The New England
Journal of Medicine

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Volume 240 JUNE 16, 1949 Number 24

AURICULAR FIBRILLATION IN NORMAL HEARTS*

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BOSTON

AURICULAR fibrillation is not always associated with organic heart disease, and its presence may be the only sign attracting the examiner's attention to the heart. All cases of auricular fibrillation are fairly readily separated into two significant clinical groups — a minor group occurring in anatomically normal hearts and a major group occurring in damaged and diseased hearts. Emphasis should be placed on auricular fibrillation occurring in normal hearts because of its excellent prognosis, since this arrhythmia is most frequently observed in gravely damaged and decompensated hearts in which the prognosis is rather ominous.

Auricular fibrillation occurring in normal hearts has been variously termed "benign," "idiopathic," "auricular fibrillation of undetermined origin" and "auricular fibrillation in the absence of, or as the only manifestation of, cardiac disease." Although this array of terms may be somewhat confusing, they are all synonymous.

In 1911 Mackenzie[1] reported cases of auricular fibrillation in which no evidence of cardiac disease could be detected, and in 1913 Gossage and Hicks[2] demonstrated conclusively that such a condition existed.

MATERIAL

The material for this report consists of a review and follow-up study of all the cases of auricular fibrillation occurring in normal hearts that were seen at the clinic during the past two decades. The basis of selection was as follows: the presence of auricular fibrillation was confirmed by at least one electrocardiogram, taken at the clinic or elsewhere. If the patient had experienced two or more attacks lasting less than seven days and characterized by a sudden onset and termination, the fibrillation was considered paroxysmal, and if the condition existed longer than seven days it was considered established. After the presence of auricular fibrillation was confirmed, the following criteria were used to rule out cardiac disease: a history excluding rheumatic fever or allied disorders, hypertension, hyperthyroidism and coronary arteriosclerosis; a physical examination excluding cardiac enlargement, thrills, organic murmurs, hypertension and evidence of hyperthyroidism; a roentgenogram of the chest excluding abnormalities of cardiac size and configuration; an electrocardiogram excluding such abnormalities as marked axis deviation, significant T-wave changes and auriculoventricular or bundle-branch block; and laboratory studies excluding positive serologic tests, severe anemia, diabetes mellitus and an elevated basal metabolism.

A series of 651 cases of auricular fibrillation was reviewed, and only 30 cases (4.6 per cent) were found to have occurred in normal hearts. Of these, 10 (33.3 per cent) were established, and 20 (66.6 per cent) were paroxysmal (Table 1). Numerous cases of transient auricular fibrillation in apparently normal hearts were noted, but were not included in this report because the conditions under which they occurred inferentially excluded a normal myocardium. This point is elaborated below in the discussion of pathology.

INCIDENCE

That auricular fibrillation rarely occurs in congenital anomalies of the heart, syphilitic heart disease and bacterial endocarditis is well known. It may be present in any form of heart disease, but is most frequently observed in rheumatic (especially mitral stenosis) and hypertensive heart disease, hyperthyroidism and coronary arteriosclerosis: these four conditions account for approximately 89 per cent of all patients observed with this arrhythmia.[3-5]

Parkinson et al.[6] found 85 per cent of their cases of paroxysmal auricular fibrillation associated with signs of cardiac disease. It is generally agreed by those familiar with the subject[7-10] that approximately 6.5 per cent of all auricular fibrillation occurs in normal hearts, the arrhythmia being established in about a third of the cases and paroxysmal in the remainder. Auricular fibrillation is most frequently observed from the fourth through the sixth decade of life, reaching a peak incidence in the fifth decade, and it occurs most frequently in men. In the group reported here most of the established cases (70 per cent) were detected or occurred

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in the fourth decade of life, and the paroxysmal (45 per cent) in the fifth. All the established cases and 55 per cent of the paroxysmal occurred in men.

Goldbloom and Segall[11] reported auricular fibrillation in an infant of 3 months whose heart was otherwise normal. Spontaneous conversion to sinus rhythm occurred at one year of age, and a ten-year follow-up study failed to reveal any evidence of cardiac disease.

Wolff[12] reported 5 cases of familial auricular fibrillation occurring in normal hearts, and stressed its benignancy so long as the ventricular rate remains slow and embolism does not occur. His patients were all athletic, enjoyed the "lesser evils" of life and lived unrestricted without the necessity of drugs. In this series, Case 24 is an example of familial paroxysmal auricular fibrillation, and both the patient and his brother have enjoyed an active,

TABLE 1. *Clinical Data in Cases of Auricular Fibrillation Occurring in Normal Hearts.*

Case No.	Sex	Age When Condition Was Detected	Duration	Associated Disease	Reason for Clinic Visit	Therapy
		yr.	yr.			
Established auricular fibrillation:						
1	M	36	17	None	Evaluation	Quinidine
2	M	39	19 (paroxysmal auricular fibrillation) 6 (established auricular fibrillation)	Chronic anxiety	Irritable colon	Digitalis
3	M	35	0.8 (paroxysmal auricular fibrillation) 11 (established auricular fibrillation)	Anxiety	Evaluation	Digitalis
4	M	51	10	Anxiety	Evaluation	Digitalis
5	M	31	15 (paroxysmal auricular fibrillation) 6 (established auricular fibrillation)	None	Evaluation	Digitalis, periodic
6	M	19	46	None	Evaluation	None
7*	M	38	26	None	Latent congestive heart failure	None
8	M	30	12	Peptic ulcer; inguinal hernia.	Peptic ulcer	Digitalis
9	M	34	45	Arteriosclerosis	Mild congestive heart failure	None
10*	M	50	11	Carcinoma of stomach	Cancer	None
Paroxysmal auricular fibrillation:						
11	F	26	22	None	Evaluation	Quinidine
12	M	43	10	Umbilical hernia	Evaluation	Quinidine; quinidine and digitalis.
13	F	30	20	Irritable colon	Irritable colon	Digitalis
14	M	41	26	Cholecystitis with stones	Evaluation	None
15	M	35	35	Nasal polyps	Evaluation	None
16	M	45	8	Chronic sinusitis	Evaluation	None
17	F	42	10	None	Evaluation	Digitalis Quinidine
18	M	48	12	Irritable colon	Irritable colon	Quinidine
19	F	51	2	Anxiety	Evaluation	Digitalis
20	F	42	22	Uterine polyps	Uterine polyps	Digitalis
21	M	53	27	Inguinal hernia	Hernia	Quinidine
22	F	38	7	Chronic nervous exhaustion	Evaluation	None
23	F	38	Years	Carcinoma of nose	Carcinoma	None
24	M	24	18	None	Evaluation	Quinidine
25	M	45	2	Anxiety (chronic)	Evaluation	None
26	F	21	3	Anxiety (chronic)	Evaluation	Quinidine
27	F	46	5	Menopause; arthritis.	Evaluation	None
28	M	43	14	None	Evaluation	Digitalis Quinidine
29	M	45	Unknown	Irritable colon	Irritable colon	Quinidine
30	M	32	5	None	Dyspnea	Digitalis Quinidine

*Diagnosis made at insurance examination. Diagnosis made by local physician in all other cases except one, which was discovered at clinic.

unrestricted existence well into their fifth decade of life without evidence of heart disease. Case 9 is of exceptional interest; the patient maintains that his pulse has always been irregular, and that all the males in his family have a similar pulse. he had auricular fibrillation. He is now seventy-nine years old and has experienced forty-four years of confirmed auricular fibrillation without symptoms, cardiac limitation or the use of drugs. His father and brother, "both of whom had had auricular fibril-

TABLE 1 (*Continued*).

CASE No.	EFFECT	SUBSEQUENT COURSE	COMMENT
1	None	Excellent health (pulse 84)	Patient asymptomatic in 1947; auricular fibrillation present.
2	Established auricular fibrillation	Patient remained nervous (pulse 80)	No evidence of heart disease in 1942
3	Established auricular fibrillation	Patient asymptomatic; no heart disease.	Pulse 70–80; no deficit.
4	Decrease in rate	Patient asymptomatic; no heart disease.	In 1948 blood pressure 100/70; electrocardiogram showed auricular fibrillation; x-ray film normal.
5	Decrease in rate	Mild congestive heart failure after 21 yr.; excellent response to treatment.	Evidence of coronary sclerosis in 1948; blood pressure 140/70.
6		Patient asymptomatic for 44 yr. and then developed mild congestive heart failure with good response to treatment	In 1948 hypertensive heart disease (blood pressure 140/80); evidence of coronary sclerosis.
7*		In 1947 latent congestive heart failure developed	In 1948 coronary sclerosis; patient asymptomatic.
8	Excessive slowing of rate; drug discontinued.	Heart normal; pulse 70; no deficit.	In 1948 heart normal; patient asymptomatic.
9		Patient asymptomatic for 44 yr.; in 1948 congestive heart failure developed; evidence of coronary sclerosis.	All males in paternal family have irregular pulse
10*		Pulse 80–90; no deficit; blood pressure 106/70.	Heart normal
11	Cessation of attacks	Normal heart	In 1948 attacks less frequent
12	No effect; conversion.	No further attacks	Paroxysmal auricular fibrillation for 10 yr.; conversion to sinus rhythm; heart normal.
13	Decrease in attacks	Heart normal after 20 yr. of fibrillation	
14		Patient died of stroke in 1946	Congestive heart failure never developed
15		Coronary occlusion in 1941 after 28 yr. of fibrillation	In 1948 no angina; patient working hard and in excellent health; fibrillation still present.
16		No follow-up; heart normal.	Patient Canadian doctor
17	None; conversion.	Last follow-up 2 yr. after conversion; no more fibrillation.	Complete cessation of attacks
18	Attacks abolished	Last follow-up 1948; no drug; no attacks; heart normal.	
19	No effect	Patient last seen 2 yr. after evaluation; heart normal; fibrillation still present.	
20	Attacks stopped	In 1944 carcinoma of rectum developed; Miles resection performed.	In 1948 no evidence of heart disease; fibrillation still present.
21	Attacks stopped	In 1943 blood pressure 160/100; heart normal.	In 1944 fibrillation still present; heart still normal.
22		Attacks short and infrequent; no symptoms.	In 1943 heart normal; fibrillation still present.
23		Patient not interested in heart	No follow-up study
24	0.2 gm. daily prevents attacks	Patient has taken quinidine for 15 yr.; attacks occur if drug discontinued.	In 1946 heart normal; patient taking quinidine (brother with paroxysmal auricular fibrillation and normal heart).
25		In 1948 no more attacks	
26	Attacks ceased	1 yr. after cessation of drug no attacks; heart normal	
27		Fibrillation continued	Heart normal after 5 yr.; no problem.
28	Attacks decreased None.	No treatment now; attacks spontaneously less frequent	In 1948, heart normal; 1 attack every 6 mo.
29	Attacks abolished	No more attacks	
30	None Attacks abolished	Heart normal; no more attacks.	Fibrillation present 4 yr. without symptoms

"This irregular pulse is a family legend passed on from father to son and is indicative of long life." The patient under discussion never visited a physician until thirty-four years of age, when he was told that lation," had led a similar existence, dying at eighty-two and seventy-eight years of age, respectively, from "hardening of the arteries." This legend is very interesting, even in the absence of confirmation.

Pathology

That auricular fibrillation occurs in normal hearts has been proved repeatedly at post-mortem examination.[8, 10, 11] Auricular fibrillation is a disturbance of auricular impulse formation and conduction that is a physiologic phenomenon and not a pathologic one. This was admirably demonstrated by Yater[13] and summarized in his conclusion: "There is no pathologic change in the heart characteristic of auricular fibrillation." The pathology is mentioned here only to emphasize its absence.

The previously mentioned transient type of auricular fibrillation occurring in severe infections (typhoid, diphtheria, pneumonia, pleural effusions and fevers) following prolonged hypoxic surgical procedures (on the brain, chest and abdomen) and in various toxic states (diabetic coma, drug intoxication, inhalation of noxious gases and deep anesthesia) was purposely excluded from this report because the etiologic agent is obvious and pathologists are all too familiar with the myocardial edema, degeneration and inflammation associated with such conditions.

Etiology

Since an anatomic lesion has been excluded as the basis of auricular fibrillation one must explore the realm of physiology for an explanation. Friedlander and Levine[7] advocated the theory of a "trigger mechanism" in which hypothalamic impulses transmitted via the vagus nerve produce the arrhythmia. Once the reflex is in motion it tends to become fixed, resulting in established auricular fibrillation unless some interference interrupts the circus movement. Other investigators working on the etiology of auricular fibrillation have presented evidence incriminating reflex vagal activity,[14] increased intra-auricular distention[15] and a combination of vagal tone and an exciting agent such as acetyl-beta-methyl-choline.[16] However, these theories were presented to explain auricular fibrillation occurring in the presence of cardiac disease and are hardly applicable to that under discussion. Auricular fibrillation is frequently produced in animals for purposes of study by intravenous mecholyl or electrical stimulation of the myocardium.

Attacks of paroxysmal auricular fibrillation may be precipitated by nervous factors, and usually a combination of several are present. The arrhythmia is frequently observed in emotionally labile persons, and in mental workers who are subjected to stress. Many of the patients reported here were emotionally unstable and suffered from anxiety, nervous indigestion, fatigue and nervous exhaustion. Undoubtedly, reflex autonomic activity plays a role, but its exact relation remains unknown. Attacks of paroxysmal auricular fibrillation were associated with a psychogenic or functional element in 70 per cent of the cases studied: 30 per cent of patients experienced attacks precipitated by anxiety, 25 per cent by indigestion, and 10 per cent by exhaustion and fatigue, and 5 per cent blamed alcohol and tobacco. Paroxysms occurred in response to any one of several psychogenic stimuli in some patients, and in a few the stimuli seemed to be additive in effect. No precipitating factor or known etiologic influence could be elicited in the cases of established auricular fibrillation.

Physiology

Auricular fibrillation is manifest by a totally disorganized multitude of fibrillary twitchings in the auricular muscle that convert it into a quivering mass of myocardium. The circus theory of auricular fibrillation is most widely accepted at the present time. Smith, Walker and Alt[17] adequately demonstrated that in auricular fibrillation with a pulse rate below 100 and a negligible pulse deficit the cardiac output is normal, and that it diminishes as the pulse deficit increases. They also found that conversion of controlled auricular fibrillation to sinus rhythm did not increase the cardiac output. These findings were true of normal hearts and damaged hearts, in the absence of valvular lesions. By direct intra-auricular measurements, Stewart, Crawford and Gilchrist[18] showed that auricular fibrillation with a nearly regular rhythm did not diminish the rate of blood flow. Buchbinder and Sugarman[19] demonstrated, by direct measurements, that the arterial blood pressure is constant in cases of auricular fibrillation with a nearly regular rhythm. Hence, in normal or controlled auricular fibrillation, the cardiac output and the rate of blood flow are not diminished and the blood pressure is constant, ensuring adequate tissue oxygenation and normal tissue metabolism. Since auricular fibrillation in normal hearts is characterized by its slow ventricular rate and negligible or absent pulse deficit, it appears to be an efficient physiologic mechanism.

Symptomatology

The symptomatology of this arrhythmia varies from an unawareness of its presence to partial incapacitation in the anxious and introspective. The group of cases reviewed here revealed that 80 per cent of the patients with established auricular fibrillation were unaware of its presence and asymptomatic, whereas the 20 per cent who experienced preceding paroxysmal attacks noted only palpitation and this symptom disappeared with establishment. It is remarkable that none of these patients were "heart conscious." Although 95 per cent of the patients with paroxysmal attacks experienced palpitation, the remaining 5 per cent were unaware of its presence until enlightened by the family physician. Other complaints associated with paroxysms were faintness, giddiness, exhaustion, slight dyspnea and anxiety. Wolff[20] reported angina pec-

toris associated with attacks, but this is rare. Syncope has also been reported but is uncommon.

The one characteristic sign of auricular fibrillation in a normal heart is the slow ventricular rate with a negligible pulse deficit in the absence of digitalis therapy. In the established group of cases reported here, all had a ventricular rate between 60 and 90 per minute with an absent or negligible pulse deficit. The absence of a pulse deficit was commented upon by the examining physician in 50 per cent of the cases. The patients with paroxysmal attacks, during attacks, had a ventricular rate between 70 and 110 per minute in 90 per cent of the cases. Since most of these ventricular rates were taken from electrocardiograms obtained during attacks, the difference between apical and radial rates is unknown.

Course and Complications

Patients with established auricular fibrillation may remain asymptomatic indefinitely. In 2 of the cases reported here it persisted over forty-four years before cardiac symptoms developed. Once established, the arrhythmia tends to remain permanently. An occasional case, however, reverts to sinus rhythm, spontaneously or under the influence of quinidine, after years of uninterrupted fibrillation.

Patients with paroxysmal auricular fibrillation may continue to experience attacks along a fairly regular course, or the attacks may become less frequent and of shorter duration, or cease — spontaneously or under drug therapy. Attacks may assume a progressive nature, becoming more frequent and of longer duration, and the arrhythmia becomes established. In such a course, digitalis is almost sure to result in established auricular fibrillation with symptomatic relief. In the cases reported here, 1 became established spontaneously and 2 by digitalis therapy; 10 cases were favorably influenced by drug therapy; paroxysms became less frequent in occurrence and of shorter duration in 1 spontaneously; and 9 continued along their usual course. Only 10 per cent of the paroxysmal cases usually become established.[6]

The duration and frequency of paroxysms are totally unpredictable. Brill[21, 22] found that 90 per cent lasted less than seven days. In the cases reported here 90 per cent of the paroxysms lasted less than twenty-four hours, and 60 per cent less than four hours.

Complications from auricular fibrillation per se are rare; however, if the ventricular rate becomes rapid with a marked pulse deficit, anginal or syncopal attacks may occur, and if this persists, congestive heart failure may supervene. Why the ventricular rate becomes rapid is unknown, but the resultant cardiac inefficiency proceeds to latent or manifest failure. This is a completely reversible type of heart failure and after decompensation responds to the accepted forms of therapy; subsequent quinidinization may effect conversion to sinus rhythm, resulting in a completely normal heart and preventing recurrence.[6, 21, 22]

In addition to the previously mentioned complications that are peculiar to this condition, the patients, if they survive long enough, are subject to the malignant lesions, degenerative diseases and overwhelming infections of senility. Like all persons with normal hearts, many of them develop manifestations of coronary arteriosclerosis, coronary occlusion and hypertensive heart disease in later life. However, some die after years of auricular fibrillation, without clinical or pathological evidence of myocardial disease.

In this group of 30 patients, 20 have been adequately followed, and 65 per cent of these still show no evidence of heart disease. In those of advanced years, evidence of coronary arteriosclerosis has developed in 4 patients, 1 of whom has experienced an infarct; hypertensive and coronary arteriosclerotic heart disease has developed in 1, and hypertension in 2 — 1 died from a stroke. In 4 of these 7 patients some degree of congestive heart failure has occurred. The average age when failure made its appearance was sixty-four and a half years, and the average duration of confirmed fibrillation prior to failure was thirty-four years. It is interesting that in only 7 of these 20 patients has evidence of heart disease developed, and in these, manifestations occurred only after years of asymptomatic fibrillation and after they were approaching senility. Three patients have carcinoma; in these cases the heart remains normal.

Diagnosis

There is usually little difficulty in determining the presence of auricular fibrillation on routine physical examination, but in all cases it should be confirmed by an electrocardiogram. Organic heart disease must be ruled out by the history, physical examination, roentgenogram, urine and blood studies and electrocardiogram. The criteria used in this study should be complied with before the diagnosis of auricular fibrillation in a normal heart is established.

Auricular tachycardia, auricular flutter and frequent extrasystoles may cause confusion on physical examination, but fortunately the electrocardiogram makes up for clinical inadequacies by vividly portraying the varying intervals between R waves and the absence of P waves.

In making this diagnosis one must beware of the young obese male, the diabetic patient and all persons in the sixth decade of life, for coronary arteriosclerotic heart disease may be concealed in these cases. Auricular fibrillation is frequently a manifestation of hyperthyroidism, and the nervous patient with a palpable thyroid gland cannot be dismissed without a thorough investigation. Rheu-

matic heart disease may also be associated with auricular fibrillation of long standing, and one must make a careful search for valvular murmurs, remembering that the presystolic accentuation of mitral stenosis often disappears in the presence of auricular fibrillation. When murmurs are present they must be carefully evaluated. The roentgenographic shadow must be carefully scrutinized for a prominent conus, and a fluoroscopic examination of the chest made to rule out a distended left auricle. A history of previous hypertension must be sought, and the axis deviation of the electrocardiogram taken into consideration.

In the group reported here, 3.3 per cent of the cases were discovered at the clinic, 6.6 per cent were discovered at routine life-insurance examinations, and 90.1 per cent were diagnosed by the family physician. It is interesting that 60 per cent of these patients came to the clinic for an evaluation of their cardiac status subsequent to the discovery of the arrhythmia, and 40 per cent came for unrelated conditions.

Prognosis

The ultimate prognosis of auricular fibrillation occurring in normal hearts is dependent upon the maintained integrity of the myocardium, and is independent of the arrhythmia. The myocardium is subject to all the stresses, inflammations and degenerative changes of life, and if these occur, the prognosis becomes that of the underlying disease. When the arrhythmia makes its appearance after the fifth decade, the patient must be followed closely for myocardial disease, which may become manifest at any subsequent time.

Clinicians are well aware of the tendency for thrombus formation and subsequent embolism in auricular fibrillation; however, their statistics are compiled from cases of organic heart disease in which the distended auricles, slowed circulation of congestive heart failure and mural thrombi of previous infarction furnish ideal conditions for such accidents. Since auricular fibrillation occurring in normal hearts eliminates the stagnant auricular circulation and mural thrombi necessary for embolism, it is doubtful if such an accident ever occurs in this condition prior to the appearance of a complicating myocardial disease.

Numerous cardiologists have commented upon the excellent prognosis[23] and benignancy of this condition and state that the incidence of cardiovascular complications, occurring only after years of fibrillation in elderly persons, and the mortality rate are that of the general population.[10, 24] They also believe that the condition is much more common than is generally recognized.[23] The benignancy of auricular fibrillation alone is exemplified by the observation that in a follow-up study of ten years or more among thyrocardiac patients who had been operated on for hyperthyroidism, the survival rate in those with established auricular fibrillation was no less than that in those with normal rhythm.[8] Master and Eichert[25] stressed the temporary incapacity resulting from this condition in military personnel; however, it is doubtful if this would occur in civilian life, except in a confirmed neurotic. The excellent prognosis of auricular fibrillation occurring in normal hearts is in marked contrast to that occurring in diseased hearts, in which the expectancy of life is two and a half to seven years.

None of the group of patients reported here ever suffered incapacity for work or recreation because of auricular fibrillation itself, and several underwent as many as three major surgical procedures without cardiovascular complications of any type.

Therapy

All these patients should receive an adequate explanation of their condition and should be reassured that it is benign. If precipitating factors can be determined in the paroxysmal type, an attempt should be made to remove them, and the patient advised to get more rest, relaxation and diversion of interests — with or without the aid of mild sedatives.

In dealing with these patients it should be remembered that the health of the majority of them will not depend on any form of drug therapy.[24] In slow, established auricular fibrillation with a negligible pulse deficit the cardiac dynamics are physiologically normal, and nothing is to be gained by conversion to sinus rhythm. The usual case of paroxysmal auricular fibrillation with infrequent attacks of short duration is definitely not benefited by therapy. However, if attacks are progressive and associated with disabling symptoms, therapy is indicated. As a therapeutic guide, attention should be focused upon the ventricular rate, for when this becomes rapid with a marked pulse deficit, cardiac efficiency is diminished, compensation is threatened and therapy is indicated. A rapid ventricular rate, and not the presence of auricular fibrillation, is the indication for drug therapy.

Two drugs, quinidine and digitalis, are widely used in the treatment of auricular fibrillation. Quinidine is the drug of choice for converting fibrillation to sinus rhythm because of its depressive action on vagal tone, cardiac muscle and junctional tissue conduction, and it will effect conversion in 65 to 75 per cent of the cases in which it is used. Digitalis and its glycosides are largely reserved for slowing the ventricular rate in congestive failure by virtue of their ability to increase vagal tone, the refractory period of auricular muscle and the time for conduction in junctional tissue. Paroxysmal auricular fibrillation of a progressive or disabling nature may be readily controlled by quinidinization to maintain sinus integrity or digitalization to establish the arrhythmia. If congestive heart failure supervenes, the patient should be placed at bed rest, given an acid-ash, salt-free diet, a normal fluid

intake, morphine, oxygen and mercurial diuretics as indicated and digitalized to control the ventricular rate and decrease the pulse deficit. After compensation is regained the arrhythmia may be converted to sinus rhythm by quinidine therapy, with gratifying and lasting results. Quinidine should not be used before compensation is restored because conversion may result in an uncontrollable tachycardia or embolism. When the manifestations of a complicating cardiac disease appear, the treatment is that of the underlying disease.

The young patient with auricular fibrillation and a normal heart is the ideal subject for quinidine therapy; however, one must weigh the benefits to be gained against the potential danger to the patient. Here the only real risk of quinidine therapy is that of sudden death from respiratory paralysis, ventricular fibrillation or cardiac arrest, and this has an incidence of about 1.8 per cent.[26] Because of its inherent risks, therapy should never be advocated for the sake of treatment. Sokolow[27] has advocated the use of quinidine routinely in patients with early auricular fibrillation and a normal heart, to prevent subsequent embolism; however, it is doubtful if such prophylaxis is justified. If quinidine therapy is to be instituted, the patient should receive two test doses of 0.09 to 0.2 gm. four hours apart, and if no untoward symptoms occur the dose should be increased by 0.2 gm. every four hours until conversion is effected or mild toxic symptoms such as nausea, tinnitus and diarrhea develop. After conversion is effected the patient should be placed on a maintenance dose of 0.2 gm. three or four times a day for a brief period, and this gradually worked down to a minimal maintenance dose, which is frequently as low as 0.09 gm. three times a day. This maintenance dose may be continued indefinitely if toxic symptoms do not appear.

In the group of patients reported here 36.6 per cent received no treatment; quinidine converted 16.6 per cent and diminished attacks in 10 per cent; digitalis established the preceding paroxysmal fibrillation in 6.6 per cent and diminished attacks in 6.6 per cent; and combined digitalis and quinidine produced conversion in 3.5 per cent. Digitalis had no effect on 20 per cent of the cases, and quinidine on 25 per cent of the cases in which they were used. One patient in this group has been on a maintenance dose of quinidine for fifteen years, and attacks still occur when the drug is discontinued.

Summary

Auricular fibrillation, established and paroxysmal, does occur in normal hearts and accounts for approximately 6.5 per cent of all cases of this arrhythmia observed. It occurs most frequently in men and may make its appearance at any age. The patient usually experiences no symptoms, or is aware only of palpitation. The only unusual cardiac finding is slow auricular fibrillation with an absent or negligible pulse deficit. This type of auricular fibrillation is physiologically reasonably efficient, maintaining an adequate cardiac output, a normal rate of blood flow and a constant arterial pressure. The etiology is unknown, but increased autonomic tone appears to play a part. Complications are rare, and the arrhythmia may persist for years without evidence of cardiac disease. The prognosis is that of the underlying myocardium, and the arrhythmia itself appears to be without significance. Treatment is not indicated unless complications develop, and the therapy is that of the complication.

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THE SCHICK STATUS OF 18,000 YOUNG ADULT MALES*

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THE incidence of diphtheria in the United States as a whole declined from 1924 to 1945. However, in 1945 there were 18,606 cases of the disease—a larger number than had been reported since 1939. The various sections of the country did not share alike in this increase. Table 1, which presents the cases during the period 1939–1947, shows that in New England, for example, the number of cases reported in 1946 was approximately three times that reported in 1943. In the Mountain states, on the other hand, the reported cases varied relatively little. The average annual case rates, also shown in the table, varied considerably from region to region during this period. The rates tended to be low in the northern sections and high in the southern and western. The relative increase in morbidity has been greatest in the areas showing lower annual case rates.

TABLE 1. *Cases of Diphtheria in the United States.**

REGION	YEAR 1939	1940	1941	1942	1943	1944	1945	1946	1947	AVERAGE ANNUAL CASE RATE per 100,000
New England	399	266	291	293	250	327	390	737	602	5
Middle Atlantic	2,524	1,597	1,310	1,127	960	856	975	1,832	1,453	5
East North Central	3,880	2,321	2,290	1,921	1,834	1,588	2,132	2,416	1,419	8
West North Central	1,582	1,197	1,204	1,062	1,292	1,411	1,617	1,813	1,117	10
South Atlantic	7,032	3,703	5,866	5,148	4,082	2,546	4,433	2,970	2,727	24
East South Central	2,766	1,639	2,023	1,750	1,570	1,797	2,554	1,735	1,490	18
West South Central	3,324	2,759	3,160	3,134	2,471	3,115	3,705	2,424	1,816	22
Mountain	1,073	825	895	734	663	706	770	792	689	19
Pacific	1,473	1,229	948	1,091	1,686	1,805	2,030	1,704	1,092	15
Totals	24,053	15,536	17,987	16,260	14,808	14,151	18,606	16,423	12,405	13

*The regions are the ones used by the United States Public Health Service and the Bureau of the Census.

This increase in the number of cases has caused a certain amount of alarm, although it has not been proved that it represents anything more than the usual cyclical behavior of the disease. Another disturbing event has been a change in the age distribution in certain areas, with a greater proportion of cases occurring in the older age groups.[1] In Massachusetts, for example, during the period 1942–1944, 43 per cent of the cases were in patients over ten years of age, whereas during the period 1932–1934 only 37 per cent of patients were over ten years of age. The aging of the population seems to have been insufficient to account for the shift in the age distribution of the cases.

The increased incidence of the disease in certain areas coupled with the shift in age distribution makes it of interest to present the results of a Schick survey among some 18,000 naval recruits carried out during the period October, 1941, to January, 1942, instigated by and performed under the direction of Captain LeRoy D. Fothergill, M.C., U.S.N.R. Since these men were drawn from all over the United States, it was believed that an analysis of their immunity status (as determined by the Schick test) by geographic area might throw some light on the causes of these phenomena. In the preliminary report of this survey by Cheever,[2] exigencies of space made a discussion of these points impossible.

The recruits, the great majority of whom were white, received their Schick tests promptly after their induction into naval service. Consequently, the results of the tests reflect civilian rather than military experience with diphtheria. As previously described,[2] the Schick test was carried out by injection intradermally into one forearm of 0.1 cc. of a standard diphtheria toxin so diluted that 0.1 cc. contained 1/50 MLD. A Moloney test was performed at the same time by the injection of 0.1 cc. of a 1:100 dilution of diphtheria toxoid into the other forearm by the intradermal route. The tests were read at the end of forty-eight hours and again at the end of one hundred and twenty hours. Data collected at the time of the test included name, age, place of birth, place of residence before and after the age of ten years, any history of an attack of diphtheria in the subject or in members of his immediate family and finally any history of active or passive immunization against diphtheria. Similar results were obtained when the material was tabulated according to place of birth, place of residence before age ten or place of residence after age ten. Therefore, only one of the residence classifications will be used here—namely, place of resi-

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dence before age ten. Table 2 presents the percentages of Schick-positive reactors in the regions composed of the states in which the recruits resided before age ten. The percentages of positive reactors are also shown for recruits residing continuously in urban or in rural areas and for recruits who migrated between urban and rural areas. An area was called urban if it had 5000 or more inhabitants. The migration history was based on the period from birth to age of induction and not on the period from birth to age ten. The age distribution of the population should be kept in mind when the results are being discussed. Forty-one per cent of the recruits were seventeen or eighteen years of age, and 44 per cent fell in the age group nineteen to twenty-three. Only 15 per cent were over twenty-four years of age.

TABLE 2. *Schick-Positive Reactors According to Residence.*

REGION	TOTALS		URBAN		RURAL		MIGRATED	
	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE	TOTAL TESTED	PERCENTAGE POSITIVE
New England	1,529	42.9	1,194	41.3	160	56.2	175	41.7
Middle Atlantic	2,674	38.7	1,990	36.0	354	49.7	330	43.0
East North Central	2,923	46.9	1,723	46.5	643	53.8	557	40.0
West North Central	2,560	50.1	734	42.0	1,342	56.9	484	43.4
South Atlantic	3,110	15.1	1,095	19.7	1,378	11.8	637	14.1
East South Central	1,668	13.1	479	16.5	868	10.6	321	14.6
West South Central	1,685	15.5	561	19.8	662	13.1	462	13.6
Mountain	636	45.4	184	40.8	251	48.6	201	45.8
Pacific	1,596	43.5	784	40.3	356	52.2	456	42.3
Totals	18,381		8,744		6,014		3,623	
Averages		34.1		35.6		33.7		31.3

Inspection of Table 2 shows that the variation between the different sections of the country in the percentage of positive reactors is very large. The South Atlantic and East and West South Central states have the lowest incidence of susceptible recruits—15, 13 and 16 per cent respectively. The percentages of positive reactors in the other regions are considerably higher. They vary from 39 per cent in the Middle Atlantic states to 50 per cent in the West North Central area. The correlation between the percentages of the population susceptible to diphtheria in this young adult group and the morbidity rates for the total population during the period 1939-1947 (Table 1) is not close. The New England and Middle Atlantic regions combine low morbidity with high susceptibility, whereas the South shows a low susceptibility combined with a high morbidity. In the West, both the morbidity rates and the susceptibility seem to be high. Presumably, these statements should not be interpreted in terms of the natural history of the disease without knowledge of the immunization programs in the various sections.

The differences between the percentages of positive reactors in urban and in rural areas can be seen in Table 2. The migrating group has been omitted from discussion, since the percentage of positive reactors in this group falls between those in the urban and those in the rural. In the northern and western sections the recruits coming from rural areas show consistently higher percentages of positive reactions. The average difference between the percentages of susceptibles in the rural and urban areas of these six sections is 12. In the three southern sections, on the other hand, where the percentage of positive reactors was found to be low, relatively larger numbers of susceptible persons were found in the urban areas. The average difference between the percentages of positive reactors in rural and in urban areas is −7.

Although it may be possible to explain the variation between the percentages of susceptible persons in the rural and urban areas of the different sections in terms of the presence of clinical disease, no entirely satisfactory explanation for the varying incidence of the disease itself is forthcoming. Doull,[3] writing in 1928, commented on the fact that diphtheria acts differently in the North and the South. He found that deaths from diphtheria occurred at a relatively earlier age in the southern than in the northern states. He also showed that in the 26 northern states with which he was working (1917–1924) deaths occurred at an earlier age in the more highly urbanized states. The same statement could not be made of the southern states, which were on the whole rural but had a relatively high proportion of deaths from diphtheria in the younger age groups. Doull concluded that infection was more widespread and consequently that frank cases of the disease not only were more common in the South than in the North but also showed a greater predilection for the younger age groups in the former area. He made no comparison between diphtheria death rates in urban and rural areas of the same states. Analysis of the death rates for the year 1922 shows that in the South the rural areas of the states had higher death rates than the urban, whereas in the North the reverse was true. These death rates refer only to the white population. Collins[4] has demonstrated that during the years 1940-1941 diphtheria mortality rates were considerably higher

in the rural areas of the South than in the urban areas. However, in the remainder of the country the differences between the mortality rates in the urban and rural areas were small and inconsistent.

Material from which comparisons of morbidity rates in the urban and rural areas of the different regions may be made is hard to find. It is possible to compute from the Navy survey the percentages of recruits giving a history of clinical diphtheria.

TABLE 3. *History of Clinical Diphtheria According to Residence.*

REGION	URBAN		RURAL	
	CASES	PERCENTAGE WITH CASE	CASES	PERCENTAGE WITH CASE
New England	36	3.0	4	2.5
Middle Atlantic	77	3.9	5	1.4
East North Central	72	4.2	18	2.8
West North Central	35	4.8	25	1.9
South Atlantic	50	4.6	40	2.9
East South Central	23	4.8	27	3.1
West South Central	37	6.6	21	3.2
Mountain	5	2.7	6	2.4
Pacific	43	5.5	9	2.5
Totals	378		155	
Averages		4.3		2.6

This percentage, which reflects approximately twenty years' experience with the disease, was found to be 3.7 for the entire group of recruits. Table 3 gives the number of cases and the percentages in the urban and rural areas of the different regions. Inspection of the table shows that the percentages are consistently greater in the urban than in the rural areas. It should be stated that the number of cases upon which the percentages are based is small and that the observations are subject to the limitations of memory.

Collins[4] gives diphtheria morbidity rates for the year 1935–1936 among residents of large and small cities surveyed by geographic section. He has shown that in these surveyed areas the diphtheria case rates were rather consistently higher in the towns and small cities than in metropolitan places in both the North and the South.

Chason,[5] in 1936, discussed diphtheria immunity in rural Alabama. He stated that children living in the centers of the towns were less liable to immunizing infection than those living in the outlying districts. He found that the percentages of Schick-negative white children varied directly with the size of family and that families tended to be larger in the rural districts. However, the 1930 census of population, from which statistics on median family size are readily available, shows that rural families in all sections of the country tend to be larger than urban, although the differences are greatest in the South.

It appears that the percentages of immune persons (negative and false positive) found in the urban and rural areas in 1942 in this young adult group follow more or less closely the distribution of clinically recognized cases of the disease during the period when they were growing up. It must be remembered that, as yet, no mention has been made of the proportion immunized in the different regions, but unfortunately, as shown below, the immunization histories in this survey were not reliable.

Cheever,[2] in his preliminary report on this material, showed that in the entire group of recruits the percentage of positive reactors varied with age. It was 27 per cent at age seventeen and increased gradually to 45 per cent at age twenty-six. Apparently, a slow loss of immunity occurs with increasing age. There is some interest in ascertaining if this increase in the percentage of positive reactors proceeds in the same way in the urban and rural areas of the different regions. For this purpose, the nine regions of Table 2 have been combined into four, and for simplicity the migrating group has been omitted since the percentages of positively reacting recruits in this group generally fall between those in the urban and those in the rural group at each age. Table 4 gives the number of recruits tested and the percentage of positive reactors at each age in the urban and rural areas of the four large regions. The percentages of susceptible persons are also shown in Figure 1. The differences between the percentages in the urban and in the rural areas at each age conform in general with the totals given in Table 2. Inspection of Figure 1 shows that the percentage of positive reactors increases with age in the urban and rural areas in each region, or, in

TABLE 4. *Schick-Positive Reactors According to Residence and Age.*

AGE	NEW ENGLAND AND MIDDLE ATLANTIC				EAST AND WEST NORTH CENTRAL			
	URBAN		RURAL		URBAN		RURAL	
yr.	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*
17–18	1,293	31.9	204	47.1	1,131	42.6	606	48.0
19–20	568	40.5	104	59.6	410	45.9	342	50.0
21–23	802	43.0	137	46.0	596	49.3	692	61.0
24–26	308	40.6	40	72.5	201	43.8	230	63.0
27+	213	45.1	29	55.2	119	47.9	115	70.4
Totals	3,184		514		2,457		1,985	
Averages		38.0		51.8		45.1		55.9

other words, the percentage of immune persons decreases with age. It is difficult to compare the trends on the basis of the graph. The amount of

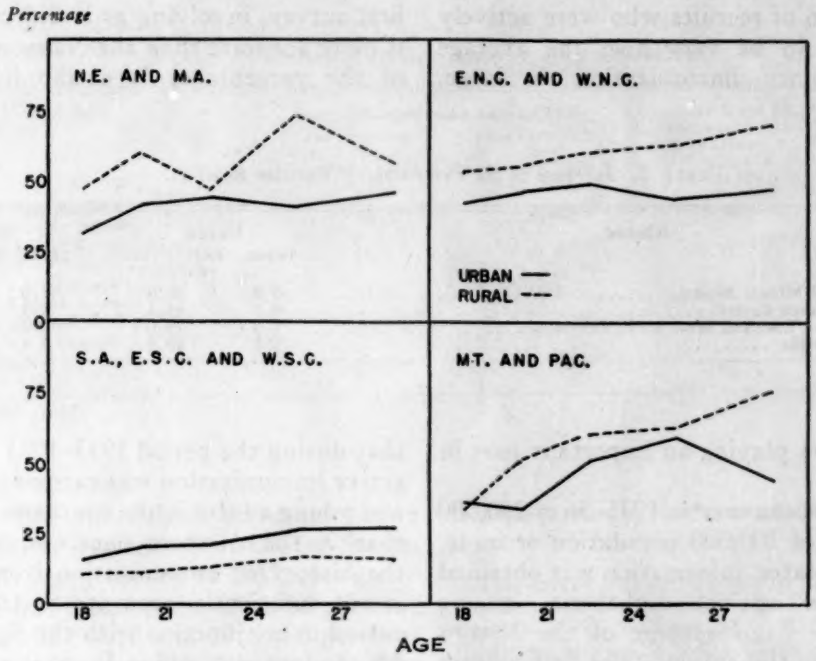

FIGURE 1. *Schick-Positive Reactors According to Residence and Age.*

increase, calculated by the method of least squares without weights, in the percentage of positive reactors per year of age is given in Table 5. Beyond the fact that they are all positive, there seems to be little that can be said in general about these trends. The percentages of positive reactors are increasing more rapidly in rural areas where the percentages of positive reactors exceed those in the corresponding urban areas, although the trends in neither the urban nor the rural areas show any relation to the corresponding percentages of positive reactors. The trends are not sufficiently well determined to show that in regions where the percentages of immune persons are high the percentages themselves decline less rapidly with age, presumably owing to more frequent contact with the organism. It may be that in the age group under consideration there is little contact with the organisms in any of the regions. In any case, it is evident that neither contact nor immunization is sufficient to keep the percentage of susceptible persons from increasing after age seventeen.

TABLE 4 (*Continued*).

AGE	SOUTH ATLANTIC, EAST AND WEST SOUTH CENTRAL				MOUNTAIN AND PACIFIC			
	URBAN		RURAL		URBAN		RURAL	
yr.	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*	*no. tested*	*percentage positive*
17-18	1,064	16.1	1,179	10.2	449	36.5	214	34.1
19-20	379	20.1	541	10.4	231	34.6	140	50.7
21-23	478	21.5	826	13.0	183	50.8	147	61.9
24-26	132	25.8	236	16.5	51	58.8	60	63.3
27+	82	26.8	126	15.9	54	44.4	46	76.1
Totals	2,135		2,908		968		607	
Averages..		19.0		11.8		40.4		50.7

It was stated above that the immunization histories in this survey are believed to be unreliable. Table 6 gives the percentages of recruits who claimed to have been actively immunized against diphtheria in the urban and rural areas of the nine regions. The numbers upon which these figures are based were given in Table 2. The percentages appear to be very low. Also included in Table 6 is the average number of years since active immunization for recruits who claimed to have been immunized. Comparison of the percentages of

recruits who were immunized with the average number of years since immunization shows that in areas where the percentages are high immunization seems to have been relatively more recent. In the New England and Middle Atlantic regions, where the proportion of recruits who were actively immunized appears to be very low, the average number of years since immunization is large. Memory seems to be playing an important part in these percentages.

In a house-to-house canvass[6] in 1935–36 of 200,000 families in 28 cities of 100,000 population or more, located in nineteen states, information was obtained about immunization against diphtheria, among other things. Table 7 gives some of the history on immunization from this survey. The first column of the table gives the regions into which the 28 cities were placed. In braces are given the corresponding regions of the Navy survey; unfortunately, the correspondence is not exact. The second and third columns give the respective percentages in the groups fifteen to nineteen and ten to fourteen years of age of people who had been immunized before 1935. The annual rate of immunization per 100 for the year 1935–1936 among subjects fifteen to nineteen years of age is given in the fourth column. The percentage of recruits seventeen to eighteen years old claiming to have been immunized in the urban population in the Navy survey of 1942 is shown in the last column. It seems that the results could not be more in disagreement. The South, which shows the smallest percentage of immunization in the 1935–1936 survey, shows the largest percentage in the Navy survey. The North East, on the other hand, was found to be well immunized on the first survey and poorly immunized on the second. Although there can be no doubt that the first survey, involving as it did careful questioning, is more accurate than the Navy survey, the reversal of the percentages is extraordinary. It suggests that during the period 1935–1941 considerably more active immunization was carried out among children and young adults in the southern and western states than in the northern ones. It is unfortunate that the history of immunization from the 1942 survey is not sufficiently accurate so that it may be discussed in conjunction with the Schick-test material, which does not suffer from the same limitations.

If the results of the 1935 survey are accepted as being more representative of the facts, collation of the information in Tables 1, 2 and 7 shows that no hard and fast statements can be made about the relations between the amount of immunization, the state of immunity as shown by the Schick test and the morbidity in the different sections of the country. The northern region in general appears to have been relatively well immunized, and yet shows a high percentage of Schick-positive reactors and a low morbidity rate. The South, on the other hand, shows a low rate of active immunization, a high level of immunity and a high morbidity rate, and the far West has been relatively well immunized, and has a high percentage of positive reactors and a high morbidity rate. It should be pointed out

TABLE 5. *Increase in the Percentage of Positive Reactors.*

REGION	URBAN		RURAL	
	TREND	PERCENTAGE POSITIVE	TREND	PERCENTAGE POSITIVE
New England and Middle Atlantic	0.9	38.0	1.0	51.8
East and West North Central	0.3	45.1	2.1	55.9
South Atlantic and East and West South Central	1.0	19.0	0.6	11.8
Mountain and Pacific	1.3	40.4	3.4	50.7

TABLE 6. *Percentages of Recruits Actively Immunized and the Average Number of Years since Immunization According to Residence.*

REGION	RECRUITS ACTIVELY IMMUNIZED		AVERAGE INTERVAL SINCE IMMUNIZATION	
	URBAN	RURAL	URBAN	RURAL
	%	%	yr.	yr.
New England	13.9	14.4	9.11	9.91
Middle Atlantic	18.8	21.2	9.22	8.22
East North Central	20.1	26.7	8.56	7.11
West North Central	25.9	25.7	7.83	7.96
South Atlantic	25.3	35.2	6.98	6.49
East South Central	31.7	32.8	7.28	7.54
West South Central	28.7	31.6	6.59	7.43
Mountain	22.8	27.5	7.14	7.66
Pacific	16.5	23.6	8.26	7.51
Averages	21.0	29.1	8.08	7.47

that the morbidity rates refer to the total population, whereas the information on immunization and the Schick status is based on young adults.

It has been the purpose here to present certain information regarding the Schick status of young adult males in different regions of the United States. On the basis of the Navy survey of 1942, this group of the population was found to be 13 to 16 per cent Schick positive in the South and 39 to 50 per cent Schick positive in the rest of the country. The percentage of positive reactors has increased with age in all parts of the country. Comment has been made upon the urban-rural distribution of the Schick-positive reactors. The young adult population of the rural areas of the North and West was found to be more susceptible than that of the urban areas, and in the South the reverse was true.

The available evidence suggests that whatever role active immunization may have played in reducing diphtheria morbidity it has had little demonstrable direct effect upon the immunity status of the general population as reflected by the results of this Schick survey. In both the North and the South the present Schick status appears to be directly related to the amount of clinical disease experienced in the last ten years. No such relation can be demonstrated in the Mountain and Pacific states, where the percentage of Schick-negative reactors is low in spite of a relatively high diphtheria morbidity. Although the incidence of clinically recognized diphtheria in the different areas of the country is not high, the low level of immunity as evidenced by the high percentage of Schick-positive reactors among young men is not a cause for complacency.

TABLE 7. *History of Immunization Against Diphtheric.*

REGION	SUBJECTS IMMUNIZED BEFORE 1935		CURRENT RATE OF IMMUNIZATION PER 100 IN GROUP 15-19 YR. OLD 1935-1936	PERCENTAGE OF URBAN 17-18 YR. OLDS IMMUNIZED*
	PERCENTAGE IN GROUP 15-19 YR. OLD	PERCENTAGE IN GROUP 10-14 YR. OLD		
North East { New England / Middle Atlantic }	52.3	61.0	0.50	16.4 20.7
North Central { East North Central / West North Central }	45.5	59.7	0.91	21.0 29.4
Intermediate { West North Central / South Atlantic }	32.9	48.3	0.46	29.4 27.3
South { South Atlantic / West South Central }	20.3	35.9	0.73	27.3 37.1
West { Mountain / Pacific }	40.8	53.1	1.49	31.0 16.0

*Navy survey (1942).

This survey was carried out by the following officers under the direction of Captain L. D. Fothergill, M.C., U.S.N.R.: Captain R. W. Babione, M.C., U.S.N.; Commander E. M. Bingham, M.C., U.S.N.R.; Commander F. A. Butler, M.C., U.S.N.; Commander F. S. Cheever, M.C., U.S.N.R.; Commander J. N. DeLamater, M.C., U.S.N.; Commander R. A. Mount, M.C., U.S.N.; Commander O. F. Munch, M.C., U.S.N.R.; Lieutenant Commander L. R. Schoolman, M.C., U.S.N.R.; and Lieutenant A. B. Smith, H.C., U.S.N. Commander L. A. Barnes, M.S.C., U.S.N., and Lieutenant (jg) Margaret Allen, W.R., U.S.N.R., helped prepare the data for punch-card analysis.

The actual survey and the preliminary statistical analysis were carried out while Dr. Cheever was stationed at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland, as a member of the Department of Epidemiology.

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THE SEQUELAE OF EASTERN EQUINE ENCEPHALOMYELITIS

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WHEN cases of eastern equine encephalomyelitis occurred among human beings in Massachusetts in 1938, it was noted that profound damage to the central nervous system led to marked sequelae. To determine whether these changes are permanent and progressive or whether improvement can be expected, all the survivors who could be located were reinvestigated. The purpose of this paper is to report the present condition of these survivors.

Since several years have elapsed since the outbreak, a few facts regarding it are given for the information of those not familiar with the previous papers.

REVIEW OF OUTBREAK

Epidemiology

In July, 1938, equine encephalomyelitis was recognized in horses in southeastern Massachusetts, 269 deaths being reported in about ten weeks.

The disease first appeared in the upper basin of the Taunton River, which drains through nearby Rhode Island, and spread to contiguous areas, particularly northeast. Approximately 70 per cent of the deaths among horses occurred in a 30-mile square extending from the mouth of the Taunton River in the south to Boston on the north, and from the boundary of Rhode Island eastward to the coast of Massachusetts. Rhode Island to the west reported 55 cases among horses, and Connecticut, 29.

Inasmuch as the rainfall in southeastern Massachusetts and Rhode Island during the summer and early autumn was unusually heavy, mosquitoes were very prevalent in these areas. Furthermore, since the prevailing winds in this area are from the southwest, the tendency of the outbreak to spread in a northeasterly direction was attributed to the fact that infection-bearing mosquitoes were carried by these prevailing winds. The movement of infected horses and the flight of infected birds may have also played a role in the spread of the outbreak.

Almost simultaneously, a very fatal type of human encephalitis appeared in the same area, largely limited to children. The median date of reported deaths in horses occurred two weeks in advance of the median date of onset for cases in human beings. Although the prevalence of the disease was much greater among horses than among human beings, the rise and fall of the outbreak in these groups were similar. There was a slow increase for four weeks, rapidly reaching the peak in two more, and then a much slower subsidence, the last case being reported sixteen weeks after the beginning of the outbreak.

The Massachusetts Department of Public Health investigated 44 cases of suspected equine encephalomyelitis.[1] From 9 of the patients, the eastern virus was isolated, and in 10 others, neutralizing antibodies for the same virus were found in the blood.[2, 3] Eight more cases were diagnosed on the basis of the clinical picture and characteristic brain lesions at autopsy.[4, 5] A diagnosis of equine encephalomyelitis was considered justified in 7 additional fatal cases because of characteristic clinical findings even though autopsies were not performed nor blood obtained for tests for neutralizing antibodies. Some patients had died before the etiologic agent had been suspected. Although 10 other cases were suspected, investigation revealed the diagnosis of equine encephalomyelitis to be unwarranted. About 70 per cent of the afflicted children were under ten years of age, the sex distribution being approximately equal. The mortality among the 34 patients was 74 per cent.

Clinical Picture

The clinical manifestations of the infection differed from other encephalitides in the greater severity of the symptoms and the high fatality. In infants the onset was sudden, but in older children and adults there were a few days of indisposition preceding active signs of encephalitis. The first complaints of older persons were commonly frontal headache and dizziness. The actual symptoms of encephalitis were almost invariably abrupt and characterized by fever, irritability, drowsiness, cyanosis and convulsions. The course of the disease was characterized by continued tremors or muscular twitchings; rigidity of the neck was constant, and a tense anterior fontanel was noted in infants, in whom a peculiar edema also developed about the eyes and in the upper extremities. A marked cyanosis was usually present, as was deep coma. The temperature was high, from 102 to 104°F., and when recovery occurred the temperature dropped by lysis over four or five days. Neutralizing antibodies appeared in the serum usually within six to eight days, and the blood showed a well marked response of neutrophilic cells. The cerebrospinal fluid was under increased pressure containing 200 to 2000 cells of which 60 to 90 per cent were neutrophils.

Surviving the acute stage, patients experienced coma and more or less rigidity of muscles for many days. Slow apparent return to normal was observed

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in a few cases, paralyses, mental changes and other residual symptoms being more frequent. Death was commonly due to encephalitis but with some terminal evidence of myocardial insufficiency or pulmonary involvement.

Pathology

The pathological changes associated with the disease in man consisted of a profound, acute, disseminated and focal encephalomyelitis characterized by intense vascular engorgement, perivascular and parenchymatous cellular infiltration and extreme degenerative changes in the nerve cells. The gross pathological manifestations were not specific.

TABLE 1. *Nine-Year Follow-up Study of Patients in 1938 Epidemic.*

PATIENT	AGE AT ONSET	SEX	RESIDUAL SYMPTOMS AT 1 YEAR	STATUS AT FOLLOW-UP STUDY	
				NEUROLOGIC	MENTAL
D. A.	12 mo.	M	Mental retardation; right spastic hemiplegia.	Right hemiplegia with spasticity and pes equinovarus	In 1945 chronologic age of 7 10/12 yr., mental age of 5 2/12 yr., I.Q. of 0.66; patient not going to school; sociable, obedient, suggestible.
R. C.	12 mo.	M	Mental deficiency; asphasia; left hemiplegia.	Left hemiplegia; aphasia; epilepsy (grand mal seizures, 2 to 7 per mo.).	Patient admitted to Monson State Hospital in July, 1942 (age 4); little or no mental development; patient deteriorated and helpless.
M. C.	18 mo.	F	Mental deficiency; marked lack of emotional control; right hemiplegia; impaired vision, partial deafness; patient speaks only a few words.	Right hemiplegia-spastic; generalized convulsions periodically.	Patient admitted to Wrentham State School in June, 1946, where chronologic age was 9 5/12 yr., mental age 1 yr., I.Q. 0.11; serious behavior problem; lack of emotional control.
D. L.	4 mo.	F	Mental retardation, strabismus, frequent convulsions	Patient died in January, 1940 at age of 2+ yr. during convulsive seizure; could not walk or sit; sixth-cranial-nerve palsy; 4 or 5 grand mal seizures per day.	Mental age of 2 mo. with chronologic age of 15 mo.
R. R.	1 mo.	F	"Decerebrate animal" and mass reflexes; eyes did not react to light.	Patient died in September, 1944; spastic flexion of all limbs; bilateral talipes equinovarus; as many as 42 grand mal and 31 petit mal seizures per mo.	Extreme mental retardation; patient deteriorated and helpless.
L. F.	8 yr.	M	Definite mental retardation (age about 3 yr.) and partial aphasia	Epileptic seizures began 1 year after acute episode and have continued since	Mental retardation; cortical test March, 1947; Hunt-Minn. 64, memory quotient, 66, vocabulary, 4, spelling grade, 3 to 4; hysterical behavior.
C. D.	6 yr.	M	Slight retardation in motor field; I.Q., 1.14.	"Slight Friedreich's foot" on left	Habit problem; patient "very nervous."
M. B.	6 yr.	F	Patient dragged one leg for first year	None	None
T. O'C.	4 mo.	M	None (at 3 mo.)	Contact lost.	

FOLLOW-UP STUDY

Getting,[6] in 1941, reported his findings in following up all 9 surviving patients of the 1938 epidemic in whose blood neutralizing antibodies for the eastern variety of virus were found. In all cases except one, this follow-up study was made approximately one year after onset. All but 3 had disabling sequelae. Six showed evidence of cerebral degeneration, with mental retardation. Three patients continued to suffer from hemiparesis, 3 from complete or partial aphasia, and 1 from emotional instability.

In carrying out a nine-year follow-up study in these patients, we have found that 2 have died (deaths attributable directly to sequelae of encephalitis); 3 have hemiplegia and mental deficiency or deterioration, with 2 requiring permanent hospitalization; 1 has chronic epilepsy with mental deficiency and hysterical behavior; in 1 neurologic symptoms, with some emotional instability, have developed; and 1 has made an apparently complete recovery so far as can be ascertained (Table 1). We have unfortunately been unable to trace 1 patient (T. O'C.). Three months after the acute episode, he showed no signs or symptoms of physical or mental impairment. Therefore, to our knowledge, 1 out of 34 patients has made an apparently complete recovery with no sequelae manifested up to this time, and another had no known defects early in convalescence when contact was lost. The mortality rate has been increased to approximately 90 per cent, with a complete recovery rate of only 3 per cent.

One can assume from this that any damage to the central nervous system during the acute phase is severe and permanent. As time goes on this damage does not improve but rather seemingly increases as more is demanded intellectually, emotionally and physically of the patients. It becomes evident that eastern equine encephalomyelitis not only is highly fatal but also carries a very poor mental and physical prognosis.

SUMMARY

The 1938 outbreak of eastern equine encephalomyelitis in southeastern Massachusetts is reviewed.

Thirty-four persons were infected, 70 per cent being under ten years of age; 9 survived, and 6 had permanent sequelae after one year. One of the 9 survivors cannot be located; 2 of the 8 other survivors have died; 4 are hemiplegic, mentally deficient and emotionally unstable; 1 is mentally deficient, epileptic and hysterically inclined; 1 has a "slight Friedreich's foot" and is a habit problem; only 1 has made an apparently complete recovery.

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HEPATITIS, EXFOLIATIVE DERMATITIS AND ABNORMAL BONE MARROW OCCURRING DURING TRIDIONE THERAPY*

Report of a Case with Recovery

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BOSTON

SINCE 1944, when Everett and Richards[1] described the anticonvulsive action of tridione (3, 5, 5-trimethyloxazolidine-2, 4-dione), the drug has been used in human beings to control epileptic attacks, especially petit mal seizures. Varying toxic reactions have been described, but to our knowledge this is the first case in which hepatic dysfunction, severe exfoliative dermatitis and leukemoid bone-marrow changes have been reported in the same patient.

The first report on the clinical use of the drug made very little mention of toxic reactions or unpleasant side effects. In 1945 Lennox[2] noted that in the majority of adolescent or adult patients, but rarely in young children, there was an unusual sensitivity of the eyes to bright sunlight. In a later report on the use of the drug in 222 patients, varying toxic manifestations were noted[3]; 122 patients showed photophobia; 32 reported a rash, either acneiform or morbilliform; 18 described gastric distress or nausea; 9 had behavior difficulty; 7 had headache; 4 noted insomnia, poor appetite and nervousness; 3 had dizziness, pain in the eyes and nosebleeds; 2 complained of sleepiness, double vision and "poor circulation"; and 1 had sneezing hiccuping and aplastic anemia. Six per cent of 127 patients showed a decrease of polymorphonuclear leukocytes below 1600. Twenty-five per cent had an eosinophil count of 6 to 25 per cent, a complete hematologic report on these cases having been presented by Davis and Lennox[4] in 1947. However, these side effects appeared to be of minor importance considering the beneficial effects in treatment of petit mal epilepsy, and the drug was sometimes rather loosely administered without due precaution. Butler[5] and Perlstein and Andelman[6] noted essentially the same relatively unimportant side reactions in later reports.

In May, 1948, Barnett, Simons and Wells[7] described for the first time the nephrotic syndrome occurring during tridione therapy. In their patient, a girl of sixteen years, edema, decreased serum al-

TABLE 1. *Studies of the Peripheral Blood.*

DATE	RED-CELL COUNT	HEMOGLOBIN	HEMATOCRIT	RETICULOCYTES	ICTERIC INDEX	WHITE-CELL COUNT	NEUTROPHILS	BAND FORMS	EOSINOPHILS
1948	*x10⁶*	*gm./100 cc.*	*%*	*%*	*units*	*x10³*	*%*	*%*	*%*
May 13	—	—	43.5	—	15	10.5	21	13	18
May 17	—	12.6	39.0	—	10	10.2	33	9	28
May 21	—	13.3	38.0	—	—	12.2	41	20	5
July 10	—	12.3	40.0	—	6	12.0	65	6	1
July 28	4.42	12.4	40.0	0.9	7	10.8	55	—	2

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bumin and elevated cholesterol reappeared on two different occasions while she was taking tridione. With the withdrawal of the drug, the blood chemical findings and nephrotic signs disappeared after several months. White[8] reported a somewhat similar case of nephrosis occurring in a seven-year-old boy who was treated with tridione.

Aplastic anemia and agranulocytosis have both been observed by several authors. Harrison et al.[9] reported a fatal case of aplastic anemia in 1946. Mackay and Gottstein[10] described aplastic anemia and agranulocytosis from tridione. A case of fatal agranulocytosis in Great Britain[11] was reported in January, 1948. Carnicelli and Tedeschi,[12] in March, 1948, discussed a fatal case of acute pancytopenia following tridione treatment in a nineteen-year-old girl, including the post-mortem findings.

In the case reported below, toxic hepatitis, a leukemoid reaction in the sternal marrow and severe exfoliative dermatitis occurred in an elderly man after the use of tridione, with recovery of the patient. It is possible that the reactions were on the basis of an allergic reaction to the drug rather than a true direct organ toxicity. It is probable that if tridione had a direct hepatoxic action this would have become evident in animal experiments, and cases of human toxic hepatitis would be much more frequent.[13]

Case Report

A 69-year-old divorced, epileptic salesman was admitted to the hospital on May 9, 1948, with a chief complaint of generalized skin rash of 5 days' duration.

The family history revealed that his mother had had epileptic attacks starting at the age of forty years. In the past year he had had nocturia, which was diagnosed as being caused by hypertrophy of the prostate. During the past few years he had had slight shortness of breath and also occasional ankle edema. In the past year he had become forgetful and lacked power of concentration.

At the age of 8 years the onset of minor and major seizures had occurred. The attacks always began with an epigastric sensation, which traveled up to his head and sometimes ended there or went on to a major seizure with unconsciousness. Convulsions were never described, but he often noticed that his tongue had been bitten and also found evidence of involuntary urination and defecation on recovery. He had had only the epigastric aura (without unconsciousness) for 12 to 15 years prior to admission, having taken phenobarbital, 32 mg. in the morning and 65 mg. in the evening. Six or seven weeks before admission he had seen a new doctor, who told him to take tridione, three (0.3-gm.) capsules a day in place of phenobarbital. About 1 month before admission, he reduced the dosage to two capsules daily. Two weeks before admission, greenish-yellow vision, which was improved by green-tinted glasses, developed. Five days before admission a generalized pruritic rash occurred and tridione was stopped. Two days later hiccuping, dark urine and anorexia began.

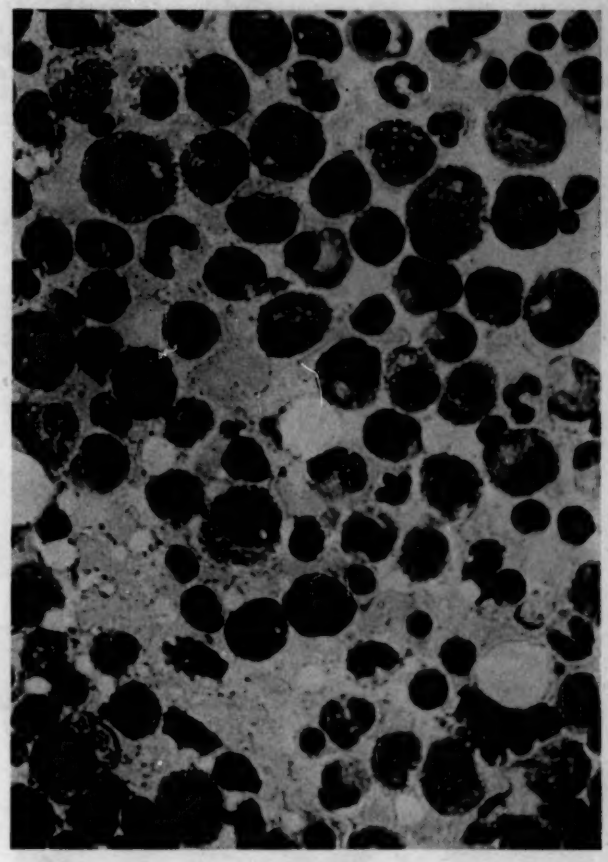

Figure 1. *Aspiration Biopsy of the Sternal Marrow Performed on March 29 (Wright–Giemsa Stain x 800).*

The marrow is markedly hypercellular, the hyperplasia including cells of both the erythrocytic and the myeloid series. There is a disproportionate increase in the more immature elements of the granulocyte series, myelocytes and metamyelocytes representing approximately 65 per cent of all leukocytes present. Plasmacytes and megakaryocytes are present in normal concentrations. Erythropoiesis appears to be active, and the progress of maturation normal in this series.

Physical examination revealed a generalized hemorrhagic, erythematous, blotchy, macular, confluent eruption involving the palms of the hands, soles of the feet, scalp, mucous membranes and lower extremities. There were numerous cervical and submaxillary small lymph nodes, and one 2-cm. node in the right axilla that was freely movable. The scleras were icteric. The pupils were not remarkable. The conjunctivas were injected. The retina showed no hemorrhages or exudates. The nasal mucosa was injected. The lips were slightly edematous and tender to palpation. The breath was fetid. A partial upper denture was present. The throat and mucous

Table 1 (*Continued*).

Basophils	Small Lympho-cytes	Large Lympho-cytes	Young Monocytes	Adult Monocytes	Myelo-cytes	Pro-plasma-cytes	Plasma Cells	Plasma Forms	Platelets
%	%	%	%	%	%	%	%	%	%
0.5	25	3.5	1	3.5	1.5	0.5	2.5	3.0	173,000
1.0	28	—	—	3.0	—	—	—	—	—
2.0	16	5.0	1	8.0	1.0	—	1.0	—	Normal
1.0	15	4.0	—	6.0	1.0	—	1.0	—	Increased
1.0	31	—	—	9.0	—	—	2.0	—	Normal

membranes were injected. The tongue was dry and coated. No distention of the jugular veins was apparent. The chest was clear to percussion and auscultation. The left border of cardiac dullness was 8.5 cm. from the midsternal line in the 5th interspace. There was normal sinus rhythm. The liver was palpable and slightly tender, and the edge was felt 7 cm. below the right costal margin on inspiration. The spleen was palpable 3 cm. below the left costal margin. Peristalsis was normal. A right reducible inguinal hernia was present. The prostate was moderately enlarged. Neurologic examination was negative except for absent patellar and Achilles-tendon reflexes bilaterally.

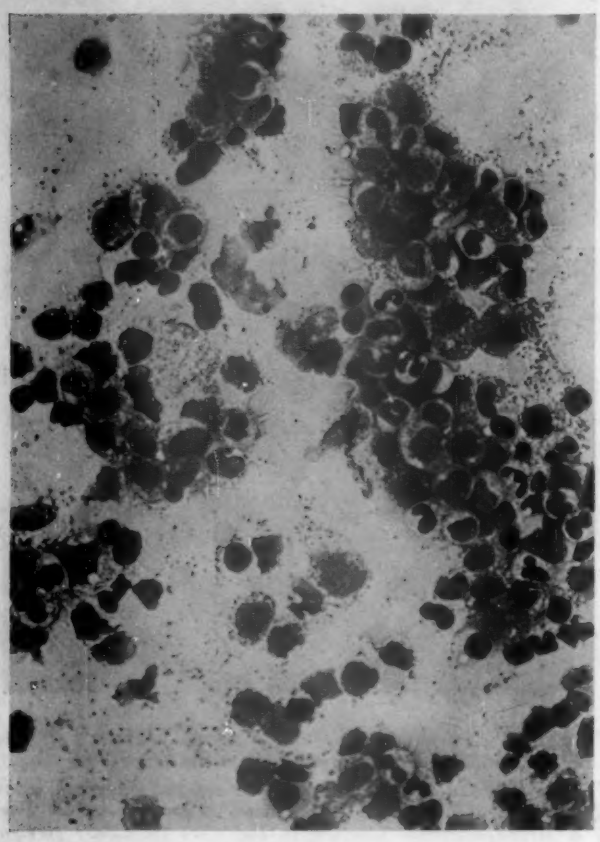

FIGURE 2. *Sternal Marrow on May 13 (x 400).*

Cellularity of the marrow has decreased to a degree approaching normal, although the relative proportions of the more immature myeloid elements are essentially unchanged.

The temperature was 100.2°F. (by rectum), the pulse 88, and the respiratory rate 18; the blood pressure was 125/75.

The urine showed a specific gravity of 1.006 to 1.022 and gave a +++ to ++++ test for bile. The urobilinogen was 1:16 on many occasions. Slight traces of albumin were noted in the sediment on several occasions. Bile was present for the first 6 days. Blood studies showed a sedimentation rate of 12 mm. per hour on admission, which rose to 47 mm. in the 3rd week and then fell to 30 mm. prior to discharge. The hematocrit was 49 per cent on admission and 34 per cent on discharge. The blood Hinton reaction was negative. The hemoglobin was 15.5 gm. on admission and 11.9 gm. on discharge. The reticulocyte count was 0.7 per cent, and the platelet count 173,000 and 144,000. The white-cell count, which was 10,500 on admission, rose to 12,200 after 3 weeks, and was 9400 on discharge. On the day following admission, the differential count was 48 per cent neutrophils, 24 per cent lymphocytes, 26 per cent eosinophils and 1 per cent basophils. The eosinophilia remained high for the first 2 1/2 weeks and then fell to within normal limits. More detailed studies of the peripheral blood are presented in Table 1.

Bone-marrow examinations were performed* on May 13 and 24 and July 28 (Fig. 1, 2 and 3), the first two of which presented evidence of markedly increased hyperplasia in the granulocytic series, and an abnormal degree of immaturity in that series; eosinophilia was likewise marked. The findings seemed consistent with those of myelogenous leukemia or severe leukemoid reaction, the latter indirectly being the correct interpretation in view of the findings obtained on the most recent examination, which must be regarded as within normal limits.

The nonprotein nitrogen was 23 to 40 mg. per 100 cc. The total protein was 5.45 gm. per 100 cc., with an albumin of 3.26 and a globulin of 2.19 gm. Prior to discharge the total protein was 7.02 gm. per 100 cc., with an albumin of 3.26 gm. The serum bilirubin on admission was 3.2 mg. per 100 cc. direct, 4.3 mg. total, and remained elevated for 3 weeks. At discharge it was 0.24 mg. per 100 cc. direct and 0.96 mg. total. The alkaline phosphatase, which was 11.76 Bodansky units initially, rose to 14.13 Bodansky units and fell to 4.89 Bodansky units by the 3rd week. Thymol turbidity was 0. Cephalin flocculation was +++. The serum amylase was 16 units and later 8 units per 100 cc. Lumbar puncture showed an initial spinal-fluid pressure equivalent to 170 mm. of water, the dynamics free, and the fluid clear and colorless; there were 43 red blood cells and 0 white blood cells per cubic millimeter, and the total protein was 40.76 mg., and the sugar 78 mg. per 100 cc., and the chloride 119 milliequiv. per liter. Heterophil-antibody agglutination was negative. The stools were guaiac negative.

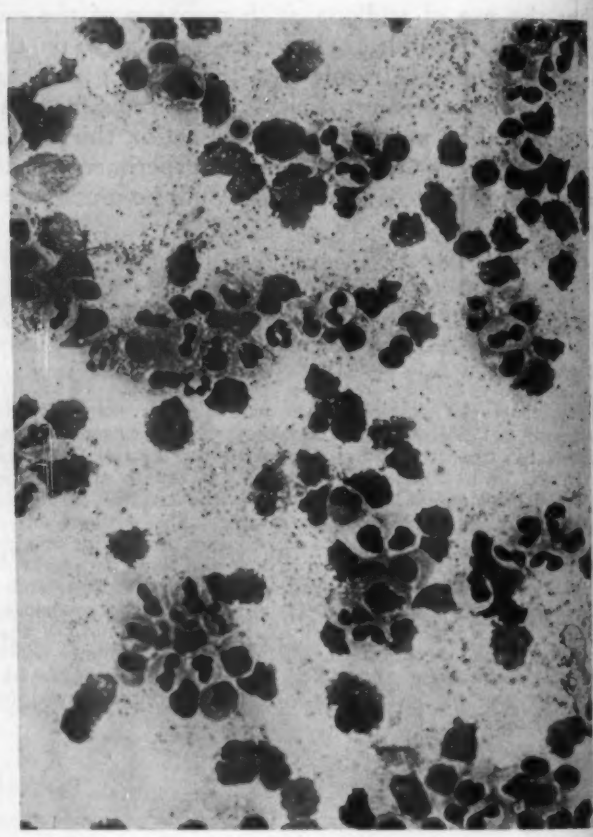

FIGURE 3. *Sternal Marrow on July 28 (x 400).*

The degree of proliferation and composition of the marrow is completely within normal limits, myelocytes and metamyelocytes now constituting approximately a third of the leukocytes present.

X-ray study of the chest revealed the heart to be normal in size, shape and position. The aorta was slightly elongated and tortuous. Both lung fields showed diffuse fibrosis and emphysema. X-ray examination of the abdomen on May 12 demonstrated a normal amount of gas in the bowel. Both kidneys were of normal size, shape and position. The out-

*Bone-marrow studies and examinations of the peripheral blood were performed by Dr. Charles Emerson, Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals.

lines of the psoas muscles were clear. An x-ray film of the skull revealed no fracture.

The clinical course is demonstrated in Figure 4. The patient was treated with a high-carbohydrate, high-protein, high-vitamin diet with supplementary vitamin B preparations. The temperature during the first day was 100 to 100.4°, and by the 3rd day it fell to 99.0° and thereafter was normal. The pulse was never above 92. The patient was given 150,000 units of penicillin daily from the 6th to the 17th day. During the first 2 days he was lethargic, and hiccups were almost continuous. Hiccups stopped after the 5th day, and beginning clinical improvement was noted. The rash remained hemorrhagic for the first 5 days and then slowly faded. Desquamation started on the 5th day and gradually extended over the entire body. By the 13th day the liver had decreased in size, the edge being felt 1 cm. to 4 cm. below the costal margin. After the 32nd hospital day the spleen was never palpable. The enlargement of the cervical and axillary lymph nodes gradually subsided so that at the time of discharge they were insignificant. The patient was discharged on June 11, improved. Follow-up study revealed that liver function, as well as his general condition, had gradually improved.

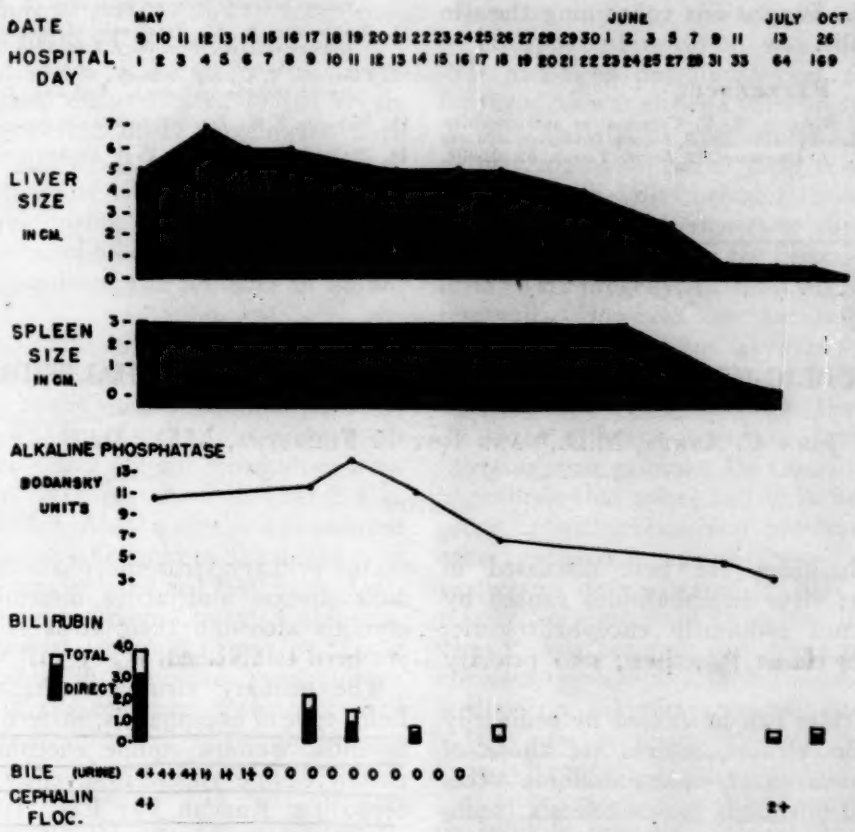

FIGURE 4. *Clinical Course.*

DISCUSSION

Tridione, a comparatively new anticonvulsant drug, has been found to be an effective agent in the treatment of petit mal seizures. It has not been shown to be effective in other forms of epilepsy. It has been demonstrated further to be potentially toxic to skin, bone marrow, and kidneys. If this is anticipated and the proper precautions taken (frequent peripheral-blood and urine examinations and careful clinical observation), tridione remains the most effective treatment currently available for petit mal epilepsy.* This opinion is supported by the experience of Dr. William G. Lennox, who has treated large numbers of children with tridione, has taken necessary precautions and has encountered little serious toxicity.

The case presented above indicates that tridione is potentially toxic to the liver also, and may stimulate the bone marrow as well as depress it. It suggests also the extreme need for careful diagnosis before tridione is used, since it appears to be effective only in petit mal attacks, whereas this patient had sensory (epigastric) seizures. Petit mal epilepsy is characterized by an onset of unconsciousness, brief in duration, *without* aura, at times with akinetic or myoclonic features. An attack, no matter how brief, that begins with any aura other than unconsciousness is not petit mal.[14] This case indicates further that tridione should not be used unless careful supervision is maintained throughout.

The toxic hepatitis in this patient responded very well to the usual treatment of hepatitis—

*Paradione (3, 5-dimethyl-5 ethyloxazolidine-2, 4,-dione), a new experimental derivative of tridione, has been found in the early experience of one of us (I.C.K.) to be at least as effective as tridione and considerably less toxic.

namely, bed rest and high-carbohydrate and high-protein diet, together with added vitamin supplements, especially of the vitamin B complex. Early recognition and vigorous treatment of any of the toxic complications of tridione may save the life of the patient.

Summary

The case of a sixty-nine-year-old man who exhibited toxic hepatitis, a leukemoid bone-marrow reaction and a severe exfoliative dermatitis after tridione therapy is reported. A review of the literature concerning the adverse reactions to the drug is presented. Suggestions concerning the use of tridione are made.

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MEDICAL PROGRESS

PUBLIC-HEALTH ASPECTS OF THE VIRUS ENCEPHALITIDES

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VIRUS encephalitides are best discussed in three groups: virus encephalitides caused by familiar viruses not ordinarily encephalitogenic; suspected, primary virus infections; and primary virus infections.

Virus encephalitides can be caused by ordinarily nonencephalitigenic viruses, which are those of herpes simplex, measles, lymphogranuloma venereum, mumps and infectious mononucleosis (probably due to a virus). Although secondary or post-infectious encephalitis has not as yet been shown to be caused by a virus, the illness occurs within a few days to a few weeks after various virus infections, such as measles, mumps, influenza, chicken pox, vaccinia, smallpox and infectious hepatitis and after vaccination against smallpox and rabies.

Suspected primary virus encephalitides are newly discovered, and their role is significant because antibodies have been found in the blood of man, and the viruses are neurotropic in laboratory animals. Clear-cut clinical infections of the encephalitic type are yet to be seen. The viruses are: West Nile, Bwamba fever, Semlike forest, Bunyamwera and Hammon-Reeves, California. The first two have been recovered from the blood of man, and the remainder from mosquitoes only. Other suspected primary virus encephalitides are von Economo's disease and acute disseminated encephalomyelitis although their virus etiology has not as yet been established.

The primary virus encephalitides are the St. Louis type of encephalitis, eastern equine encephalomyelitis, western equine encephalomyelitis, Venezuelan equine encephalomyelitis, Japanese B encephalitis, Russian Far East (tick-borne, spring-summer) encephalitis, acute hemorrhagic meningoencephalomyelitis (leukoencephalitis), lymphocytic choriomeningitis, pseudolymphocytic choriomeningitis, swineherd's disease, louping ill, acute encephalitis due to rabies and the Sabin B virus. The first six are known as the summer, or epidemic, encephalitides; the remainder are endemic virus encephalitides.

The epidemic encephalitides are a greater public-health problem than most of the others. They tend to be more numerous and present difficult problems in control, because the reservoir of the virus is usually a lower animal and the viruses are spread to man by arthropod vectors. This paper is limited to a discussion of these six virus infections.

St. Louis Encephalitis

The St. Louis epidemic of 1933[1] was up to that time the largest localized encephalitis epidemic recognized in North America. In summing up the

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epidemiologic data at the end of the 1933 epidemic, Leake et al.[2] reported that either mosquitoes were involved as vectors, or the infection was spread by contact. Mosquito transmission in the laboratory was attempted at that time but failed.[2] Since the original outbreak in St. Louis, other encephalitis epidemics have been recognized as predominantly due to this virus,[3, 4] and there have been mixed St. Louis and western equine outbreaks.[3, 5-10] Interesting to note with this is that horse infections, both of clinical and of inapparent nature, have been produced by the inoculation of the St. Louis virus.[11-13] Antibodies to the St. Louis virus have been found in the serums of normal persons and of those convalescent from encephalitis in many parts of the United States and even in Africa.[3-10, 14-17] Antibodies have also been demonstrated in the serum of horses and of numerous other vertebrates, both domestic and wild.[8, 9, 12, 16, 18-21] Blattner and Heys[22] reported the occurrence of 10 to 16 cases each year in the St. Louis area during the nonepidemic years 1939-1944, with a total of 88 cases during the seven-year period, and postulated the presence of an endemic focus.

In recent years, various investigators working both in the field and in the laboratory have established the mosquito as the vector. Hammon, Reeves et al. isolated the St. Louis virus from eight pools of naturally infected *Culex tarsalis* mosquitoes from the Yakima Valley, Washington, 3 in 1941,[23] 4 in 1942,[24] and 1 in 1944.[24] Also, a strain was isolated from *C. pipiens* (Linnaeus) caught in Washington in 1942,[24] and a strain was isolated in 1944[24] from *Aedes dorsalis* (Meigen) caught in Kern County, California. The latter was the first isolation of the St. Louis virus from any source in California even though serologic evidence of the presence of the virus had been repeatedly obtained.[5, 10, 25] Although no tests of the vector ability of *A. dorsalis* had been made in the laboratory, transmission had been demonstrated by four other species: *A. lateralis* (Meigen), *A. taeniorhynchus* (Wied), *A. vexans* (Meigen), and *A. nigro-maculis* (Ludlow).[26] A Japanese report in 1940[27] recorded the transmission of the St. Louis virus by *C. tritaeniorhynchus* (Giles) and *A. albopictus* (Skuse), in addition to the previously reported *C. pipiens* (var. *palleus* Coq).

Studies on the feeding habits of the suspected mosquito vectors in Washington,[28] Nebraska[29] and California[30] confirmed the fact that the two Culex mosquitoes found infected fed predominantly on fowl. Detailed studies[31] on inoculated chickens in 1945 showed that a very high dilution of St. Louis virus, representing only a 50 per cent end-point dose for a mouse by the intracerebral route, when inoculated subcutaneously gave rise regularly to virus in blood in a titer greater than that inoculated, usually for two or three days. No mammal tested up to that time had proved to be as good a potential source of mosquito infection.

In spite of this apparently satisfactory and well established concept of the mosquito-fowl-mosquito cycle, the epidemiology of this disease seemed to be incomplete, for the chicken and other birds tested showed no evidence of serving as chronic or latent carriers of the virus. Hibernating *C. tarsalis* and *C. pipiens* collected during winters in Washington[24] and California[30] had not been found infected even though 5429 mosquitoes were tested. Furthermore, eggs and progeny of infected *C. tarsalis* and *C. pipiens* were tested only to yield no evidence of transovarian passage of the virus. Therefore, knowledge of the true reservoir and the location of the virus during the winter and during seasons of no apparent infection was still quite vague.

It had been postulated that the true reservoir for the virus was either a vertebrate or an arthropod. A wide variety of vertebrates inoculated by the dermal routes failed to yield results suggesting a true reservoir. Blattner and Heys,[32] in 1944, however, found that *Dermacentor variabilis* (Say) was capable of transmitting the infection and of passing it on to its progeny, thereby suggesting a potential reservoir. However, no naturally infected ticks have been found; nor have any of the stages of *D. variabilis* been found upon fowl. In 1945, Smith, Blattner and Heys[33] isolated the St. Louis virus on three different occasions from chicken mites (*Dermanyssus gallinae*, De Geer). Working on the hypothesis that mites and ticks belong to the same order of arthropods and are known to transmit other pathogenic agents transovarially, these investigators demonstrated in 1947 the transovarian transfer of infection by mites infected with the virus.[34] Furthermore, the virus was isolated from chickens exposed to infected mites, and fresh mites feeding on infected chickens became infected.

It is now generally accepted that the St. Louis virus is frequently transmitted to man by mosquitoes that have become infected, in most cases by feeding on recently infected fowl. However, the true reservoir or winter carry-over mechanism has stil not been definitely ascertained. Other ectoparasites of birds, such as ticks and mites, may be the unknown factor.

American Equine Encephalitides

In Horses

For many years in Europe a mild form of equine encephalomyelitis of horses has been known as Borna disease. The causative agent was demonstrated to be a filterable virus in 1924.[35] Similar symptoms have been observed among horses for a number of years in the United States. The Kansas-Nebraska horse plague of 1912 was probably a related disease. However, the first recognized American epizootic of horses similar to this condition occurred in the San Joaquin Valley of California in 1930, when the identity of the disease was established by Meyer, Haring and Howitt,[36] who isolated

a filterable virus from the brain of 2 horses that had died from the disease. The virus was found to be immunologically different from that of Borna disease and became known as the western variety of the equine encephalitis virus.

During the early 1930's, the disease extended rapidly eastward, recorded cases reaching the peak numbers of 173,889 in 1937 and 184,662 in 1938.[37] In 1939 the western type of virus was found as far east as Kentucky, and in 1940, it was identified in Alabama,[38] and in 1941, in Michigan.[39] Up to 1944 the western type of virus had been identified in 19 states.[39, 40]

In 1933 a highly fatal form of encephalomyelitis appeared in several states along the Atlantic Coast, particularly New Jersey and Virginia. The virus from these equine cases was found to be different immunologically from the previously isolated western strain[41-43] and was therefore designated as the eastern type of virus. In 1940 it was identified in Alabama,[38] in 1941, in Texas,[44] in 1942, in Michigan,[39] and in 1944, in Louisiana and Missouri.[40] Up to 1944 the states from which eastern virus had been identified totaled 15. Thus, it became apparent that the eastern virus was no longer confined to the eastern seaboard but had spread to involve the Gulf Coast states, Michigan and Missouri. Furthermore, both eastern and western types have been identified in Michigan, Texas and Alabama (Table 1).

TABLE 1. *Distribution of Equine Encephalomyelitis among Horses in the United States (1944).**

WESTERN VIRUS	EASTERN VIRUS	BOTH TYPES
Alabama	Alabama	Alabama
Arizona	Connecticut	Michigan
California	Delaware	Texas
Colorado	Florida	
Idaho	Georgia	
Illinois	Louisiana	
Iowa	Maryland	
Kansas	Massachusetts	
Kentucky	Michigan	
Michigan	Missouri	
Minnesota	New Jersey	
Montana	North Carolina	
Nebraska	South Carolina	
Nevada	Texas	
North Dakota	Virginia	
South Dakota		
Texas		
Utah		
Washington		

*Based on data of Shahan and Giltner.[40]

The countries adjoining the United States have had the same immunologic types of virus that are known to occur in this country. The western virus has prevailed in Canada, except for a limited number of sporadic cases due to the eastern virus in Ontario.[45, 46] The western virus has been identified in Argentina,[47, 48] whereas the eastern virus has been reported from Mexico,[49] Panama,[50] Brazil[51, 52] and Cuba.[40]

In Man

Karl Meyer,[53] in 1932, was the first to suspect that an unusual encephalitis contracted by men working with infected horses might be due to the virus of equine encephalomyelitis. Examination of the brain of a ranch hand who died of the disease showed pathologic lesions similar to those observed in horses; however, this clinical impression was not proved by isolation of the virus or by the presence of neutralizing antibodies in the serum of the infected persons.

In August, 1938, an epizootic of considerable proportions occurred among horses in southeastern Massachusetts. At about the same time a very fatal type of encephalitis among infants and children made its appearance in the area. From a child dying in the Children's Hospital of Boston, Fothergill and his associates[54] isolated a virus that was identified by cross-protection tests as the virus of eastern equine encephalomyelitis. This was confirmed for the same case and 4 others by Webster and Wright,[55] who used the complement-fixation test. In patients who recovered Fothergill confirmed the diagnosis by neutralization tests. During the same month Howitt[56] isolated the virus of the western type from the brain of a twenty-month-old child dying in California. Furthermore, the blood of several persons in California who had recovered from encephalomyelitis was shown to contain neutralizing antibodies for the western virus. Thus, it was established that both known American types of equine encephalomyelitis could infect man.

Since then, the Manitoba (Canada),[57-59] Minnesota and Dakota epidemics of 1941,[60, 61] and the annual outbreaks in the Yakima Valley[7, 8, 24, 25] and in Kern and Fresno counties in California[10, 25] have attested to the ever-increasing importance of this disease. The 1941 epidemic in and around North Dakota was the largest ever recorded, with 1080 cases and 96 deaths.[61] In Manitoba that same year, 509 cases were recognized.[58] In all the areas mentioned above, the western virus was found to be the causative agent. During 1941 in Texas an epidemic of the eastern type occurred, during which repeated isolations of the virus were made from horses,[44, 62, 63] and a number of probable human cases were later revealed by mass serologic studies.[16, 63, 64]

Transmission

In 1933, Kelser[65] first proved that the virus of equine encephalomyelitis could be transmitted by the mosquito *A. aegypti*. In the succeeding few years, several workers[66-68] confirmed the work of Kelser definitely incriminating the Aedes as potential carriers of both eastern and western types of equine encephalomyelitis. Davis,[69] in 1940, reported on the ability of five species of Aedes mosquitoes native to Massachusetts to transmit the

virus of eastern equine encephalomyelitis. Hammon et al. isolated the western type from free living *C. tarsalis* five times in 1942[23, 26] and forty-one times in 1943[24] from collections made in the Yakima Valley, Washington, twenty-eight times from the San Joaquin Valley, California, in 1943[30] and once from eastern Nebraska in 1943.[29] Kitselman and Grundman[70] recovered the western type virus in 1940 from a cone-nosed bug (*Triatoma sanguisuga*, Le Conte) in Kansas. Sulkin, in 1945,[71] reported the recovery of the western virus from the chicken mite, *Dermanyssus gallinae*, and Reeves et al., in 1947,[72] recovered the western type from wild bird mites (*Liponyssus sylviarum*) in California. Syverton and Berry[73, 74] have been able to transmit the western virus by ticks (*Dermacentor andersoni*).

Significant findings have directed attention toward fowl, both wild and domestic, as representing the most common intermediate host in the cycle of infection.[75] Repeated isolations of both eastern and western strains of virus from various species prove that they may experience a specific infection usually of a mild or subclinical nature.[69, 70, 76-82] Overwhelming evidence of incriminating fowl as the major inapparent reservoir has been advanced by the large-scale serum surveys of Howitt,[5, 83] Howitt and van Herick[21, 84] and also Hammon and his associates.[31] The serologic evidence suggests strongly that, in Washington and California, infection rates with western equine encephalomyelitis are higher in birds than in mammals. In these areas, the chick has frequently been found to possess antibodies, and since it can easily be infected experimentally, it is thought to be one of the principal sources of mosquito infection if not a true reservoir or latent carrier. However, in Nebraska no antibodies were detected in any of the chickens or pheasants tested. In Texas only 8.5 per cent of the domestic fowl were positive for western equine antibodies.[31] Cox, Jellison and Hughes[80] found an infected deer in North Dakota in 1941, and McNutt and Packer[85] an infected hog.

Recovery of viruses from species of mosquitoes habitually feeding on avian hosts has established the significance of the mosquito-fowl-mosquito cycle of infection, man or horse representing merely the accidental host. However, insect vectors and also the reservoirs of infection may differ from one section of the country to another. Furthermore, as with St. Louis encephalitis, the winter carry-over mechanism has still to be definitely ascertained, although the isolation of the western type of virus from mites capable of transovarian transmission may be the answer.

Venezuelan Equine Encephalomyelitis

Kubes and Rios[86] and Beck and Wyckoff[87] isolated a virus from cases of equine encephalomyelitis from Venezuela in 1938. The infection had been recognized also in Colombia,[88, 89] Ecuador[75] and Trinidad.[90, 91] Several early reports reviewed by Gallia and Kubes[92] suggest that cases may have occurred in man in the epidemic areas. In 1943, 2 fatal cases, with subsequent isolation of the Venezuelan virus from brain tissue, were recorded.[91, 93] One of the cases preceded[91] and the other occurred during[93] an epizootic among horses and mules in Trinidad, B. W. I. In 1942 mild infections developed in 2 laboratory workers in New York[94] and in 1943, 8 laboratory workers in Rio de Janeiro had a similar illness.[95] Gallia and Kubes,[92] examining the serums of laboratory workers at the Institute of Veterinary Research in Caracas, Venezuela, found high titers of neutralizing antibody against the virus in 10 of 16 persons, only 1 of the 10 having typical symptoms.

Epidemiologically, mosquitoes have been incriminated in the natural equine infections with this virus,[96] and several potential vectors have been demonstrated.[96, 97] Gilyard found *Mansonia titilans* (Walker) infected in Trinidad and demonstrated experimental transmission with the same species.[96] Spread probably occurred from Ecuador to Trinidad, and it is easy to conceive of its spread by ship or plane or by island hopping to the Gulf Coast of the United States, where *Mansonia titilans* is already present.

In the New York and Brazilian reports,[94, 95] the virus was isolated from the blood of 7 of the 10 laboratory cases (5 on the second day of illness, 1 on the third, and 1 on the fifth). Virus was also isolated from the nose or throat washings in 2 cases (both on the second day of illness). Koprowski and Cox,[98] in 1947, reported 4 cases of laboratory infection, in 2 of which there had been no direct contact with the virus prior to infection. Furthermore, the virus was isolated from the circulating blood in 3 cases and from the throat washings in 1.

Japanese "B" Encephalitis

The name Japanese "B" encephalitis was originally used to distinguish it from the von Economo type, which the Japanese called type "A." The former is an epidemiologically and clinically distinct type of epidemic encephalitis that frequently occurred in Japan in the late summer. It has probably occurred in epidemic form in Japan proper since the beginning of this century, or quite possibly even thirty years previously. However, not until the great epidemic of 1924, involving over 6000 persons with 3797 reported deaths, did it attract much attention. Since then, annual epidemics have been recorded, sometimes from numerous regions. Between 1924 and 1937, from Japan alone, 21,355 cases with 12,159 deaths were reported.[99] Case mortality rates have ranged from 42 to 74 per cent, but have averaged about 60 per cent. Epidemics or sporadic cases have also been reported from Formosa,[99] the southern Ryukyu Islands,[99] eastern China[100, 101] and the eastern part of the

Soviet Union.[102] Smithburn and Jacobs[17] stated that, as a result of serologic tests, "the St. Louis and Japanese 'B' viruses have been active over broad expanses of territory in Central Africa," and Sabin[103] in 1943 reported a number of positive serologic tests for Japanese "B" virus in the Cincinnati area.

In the summer of 1945, an epidemic of encephalitis occurred among the native population on Okinawa and the adjacent islands[104] and was diagnosed as being of the Japanese "B" type by the complement-fixation test.[105] A total of 127 cases was found. However, it was believed that this number may have represented only 15 to 30 per cent of the total[106] because special conditions precluded discovery of all cases. At the same time, there were 38 cases of suspected virus infection of the nervous system among the American military personnel.[107] A definite clinical diagnosis of encephalitis was probably justified in only 12 of the cases, but a specific serologic diagnosis was established only in 9 and a diagnosis by other methods in 2 fatal cases.

This outbreak gave an excellent opportunity for the study of the epidemiology of the Japanese "B" encephalitis. Following the pattern of the work done on St. Louis and Western Equine Encephalitis, a search for vertebrate hosts infected with Japanese "B" virus was made. Horses, a cow and 3 goats were found to have neutralizing antibodies,[107, 108] but none of the chickens taken from the epidemic area showed evidence of infection. Furthermore, either few or no mites could be found on these or other chickens in the encephalitis zones.

Japanese[109] and Russian[110] investigators have reported the isolation of Japanese "B" encephalitis virus from *C. tritaeniorhynchus* and *C. pipiens* (var. palleus) mosquitoes caught in nature. These mosquitoes as well as *A. togoi*, *A. albopictus* and *A. japonicus*[111, 112] were demonstrated experimentally to be potential vectors. Reeves and Hammon,[112] in 1946, further showed the ability of six species (*C. quinquefasciatus*, *C. tarsalis*, *A. dorsalis*, *A. nigromaculis*, *Culiseta incidens* and *C. inornata*) of the California mosquitoes to transmit the Japanese "B" virus to animals and have demonstrated the presence of the virus in the blood of inoculated chickens.[113] Domestic animals have also been infected experimentally.[114] Fear has been expressed that, once introduced into any areas where the American types of encephalitis now propagate, the Japanese "B" encephalitis might become a "greater plague than any we have at present."

Before and during the Okinawa epidemic of 1945, *C. quinquefasciatus* was in abundance and most readily found[107]; however, tests on three pools did not yield any virus, nor were any chickens, which are known to be bitten by this mosquito in the United States, found infected. It was postulated, therefore, that some other mosquito, biting larger domestic animals and human beings, was a vector on Okinawa. The real reservoir of the virus was not found, and it was again suggested that the vertebrate hosts and possibly the invertebrate vectors varied from one area to another.

Russian Spring–Summer Encephalitis

For the past forty years, at least, an epidemic type of human encephalitis has been occurring annually in the forest regions of the Far East, Siberia and the European part of the Soviet Union, the Urals, Karelia, West Ukraine and White Russia. It occurs only during the spring and early summer, coinciding with the activity of ticks. Russian investigators have reported the isolation of the etiologic virus from man, rodents and ticks.[115-119] They have also demonstrated conclusively the tick-wild-animal-tick cycle and the tick-tick transovarian cycle, with man as an accidental or incidental host.

Studies on the virus itself made in this country by Casals and Webster[120, 121] have shown it to be very similar or identical with the virus of louping ill of sheep in Scotland, also known to be tick borne. Silber and Shubladse[122] reported in 1945 that louping ill is the tick-borne encephalitis of the western part of the Soviet Union, but that a different virus is responsible for the tick-borne encephalitis in the far eastern area. The tick is both a vector and a reservoir so that accidental transportation of infected ticks, as has already been accomplished for experimental purposes,[121] might easily establish this infectious agent in the tick areas of the United States.

Laboratory Diagnosis of the Encephalitides

Virus neutralization and complement-fixation tests are important not only because they can be used diagnostically to establish the titer of antibody in blood but also to determine the prevalence of the disease and the geographic dissemination of its virus. With a known virus, its specific antibody can be demonstrated, and with a known antibody, the identity of a virus can be revealed.

Neutralization Test

The presence of significant amounts of neutralizing antibody indicates previous infection by a virus, even though there may have been no apparent disease. This factor is the basis of the "two or three phase" test. Under ideal conditions, a specimen of serum obtained as early as possible during the acute phase of illness, another one or two weeks after onset, and a third, if necessary, taken still later, three to eight weeks after onset, are subjected to the neutralization test. Since infection by a virus may be clinically inapparent, normal persons may show specific neutralizing antibody[57, 123-125]; hence, a single positive specimen may be misleading, especially if the person has lived in endemic areas. The reason for selecting the intervals from the earliest time to eight weeks after

onset for test is that this antibody appears at varying times after infection with different viruses. In western equine virus infections, neutralizing antibody appears as early as the fourth day after onset, and in St. Louis and Japanese "B" encephalitis from three to seven days to as late as three weeks.

The success of virus neutralization as a diagnostic procedure depends upon the precision with which, in the comparison of serums obtained in the acute and convalescent stages of infection from the same patient, a definite increase of antibody in the later sample is revealed. To measure this increase in antibody (or in the protective power of an antiserum), one of two methods may be used: undiluted serum is tested against varying quantities of virus[126]; or graded dilutions of serum against a specific quantity of virus.[127]

There are two choices of laboratory recipients for serum-virus mixtures when the neutralizing capacity of a serum is to be tested: the serum-virus mixtures are injected into an animal that is uniformly and highly susceptible (that is, for encephalitis viruses, generally the albino mouse); or the mixtures are injected into developing chick embryos.[128] As a rule, the latter technic merely supplements the former or is used only for special purposes.

The specificity of the neutralization of a virus by its antiserum is generally accepted. However, there are records of cross reactions, but these occur between viruses that have common characteristics, which are reflected by common antigenic complexes. The cross reactions (also encountered in complement-fixation tests) between West Nile, St. Louis encephalitis and Japanese "B" encephalitis viruses indicate a relation of the three infections.[129-131] The serologic cross reactions are not pronounced, and laboratory workers circumvent this obstacle by utilizing the fact that the homologous reactions are usually at a definitely higher level, especially when the virus antibody mixture is injected intraperitoneally or subcutaneously. More decided cross reactions (neutralization, complement fixation) occur between louping ill and Russian Far East encephalitis viruses. However, homologous titers are always higher and cross-resistance tests by intracerebral injection exhibit definite differences between the two.

Complement-Fixation Test

Prior to 1937, several workers attempted to apply the complement-fixation reaction to the study of neurotropic viruses. The results were unsatisfactory owing to a lack either of specificity or of appropriate controls. The material from which the complement-fixing antigens are derived consists of tissue extract in which the extraneous material sometimes outweighs the specific antigen. This extraneous material can mask the results of the test, either by its anticomplementary effect or by its capacity of combining with test serums to produce nonspecific reactions. In 1941 Casals and Palacios[132] demonstrated the practicability of the test for diagnosis of several neurotropic viruses, using brain-tissue suspensions as a source of antigen. Their method is still employed, with some modifications, and consists of emulsifying infected mouse brain tissue and then centrifuging it. The supernatant is then alternately frozen and thawed until flocculation takes place, when it is centrifuged again. This supernatant contains the antigen, which is highly virulent and can be inactivated by ultraviolet irradiation[133] or by heating at 60°C. for thirty minutes.[134] Other methods of preparation of antigen are the low-speed centrifugation of infected chick embryos with inactivation by ultraviolet radiation,[135] and the extraction with benzene from infected chick embryos or mouse brains with inactivation by 0.05 per cent formalin.[136]

In preparation of animal hyperimmune (positive control) serums, it was found that the injection of tissue extracts derived from one animal species into another animal species made possible the development of confusing species or organ-specific antibodies.[132, 137, 138] Fortunately, the tissue component responsible for nonspecific reactions[139] was found sedimentable at 20,000 r.p.m. In some species this antibody-like substance is thermolabile,[132, 138] being totally destroyed at 65°C.

It was also found that human Wassermann-positive serums gave, as a rule, a nonspecific reaction with brain extracts[132] and benzene-extracted antigens[136]; however, this is overcome by heating of the serums at 65°C. for twenty minutes.

Since this information became available, the complement-fixation test has become a more satisfactory test for diagnosis of neurotropic virus diseases. However, it has not as yet been accepted for general use as has the neutralization test.

Obtaining and Sending Serum to be Tested

Persons should be bled for test serum after several hours of fasting (usually in the morning before breakfast) and with sterile technic. After 20 cc. of blood is withdrawn, it is allowed to stand for half an hour at room temperature and to clot. Then, after having been centrifuged at 2500 r.p.m. for twenty minutes, clear serum is pipetted off. If a preservative is necessary a 1:50,000 dilution of phenyl mercuric borate can be added (or 1:2,500 borate stock, 1 drop to each 1 cc. of serum, as an estimate). The serum is placed in a hard glass ampoule, which is sealed. If a test tube is used, it should be closed with a cork or rubber stopper, and the top should be completely waxed. A glass container should be filled only to a third of its volume to prevent bursting during freezing. The container is kept at about −76°C. by carbon dioxide snow until tested. It should be sent to the designated laboratory by the fastest method, preferably in a vacuum jar holding solidified carbon dioxide. If this refrigerant is not available, the

serum should be sent fluid, provided it can reach its destination within thirty-six hours.

Prevention of Virus Encephalitides

Prevention in this group of diseases consists of vector control and vaccination. With so many species of animals and birds susceptible to the viruses and with the disease occurring among them in nature, control of the primary and secondary hosts is difficult. However, much can be done in the way of vector control on a community-wide scale, and individually. Since the mosquito is apparently the major vector, modern mosquito-control procedures on a community basis should afford some protection during an outbreak. Also, individual measures, such as adequate screening of houses, avoidance of exposure to mosquitoes, and the use of new insecticides and repellents, should be carried out during an epidemic.

The observation of Higbie and Howitt,[140] in 1934, that equine encephalomyelitis virus may be cultivated in ten-day-old developing chick embryos provided the basis for subsequent work[141-147] on the preparation of formalin-inactivated vaccines effective in establishing active immunity in horses and mules. The earlier vaccines had consisted of inactivated virus in suspensions of brain tissue from animals infected with the appropriate virus.

Although such vaccines are satisfactory for administration to horses, their high content of chick tissue and egg components makes them potentially dangerous as human prophylactic agents. From 1941–1943, approximately 6103 persons were vaccinated in Manitoba against western equine encephalomyelitis, with relatively mild reactions in general and no fatal results.[88, 124, 125] During the outbreak of Japanese "B" encephalomyelitis on Okinawa in 1945, 60,000 to 70,000 military personnel received mouse brain vaccine with only three reports of a form of "neuritis" of a questionable character and 19 allergic reactions suggesting sensitivity to formaldehyde.

In the following summer, 250,000 additional persons were vaccinated with only three reports of infectious polyneuritis, which was in no way different from that occurring among unvaccinated personnel in the Far East.[107] Furthermore, the Russians have effectively used a formalinized tissue vaccine to protect man in epidemic areas.[148]

Randall et al.,[149] in 1947, prepared a purified formalinized vaccine against eastern, western and Venezuelan viruses and demonstrated upon guinea pigs active immunity against homologous types of virus, even when injected directly into the brain. Moreover, antibodies neutralizing the eastern virus were demonstrated in the serums of guinea pigs after the administration of the eastern type of vaccine and in the serums of human beings after the injection of a mixture of eastern and western types of vaccine. Usually two doses are given a week apart and neutralizing antibodies appear one or two weeks after the first inoculation. These injections should be given annually.

There is seldom valid reason to recommend the vaccination of the entire group of susceptible human beings in a community against encephalitis. Anyone who, by reason of his work, must be heavily exposed to mosquito bites in an epidemic area should be permitted the protection of the vaccine. However, whether general or extensive vaccination of the most susceptible groups (infants and those over fifty) or military personnel is advisable should be decided by those in charge of public-health adminstration who can weigh various factors involved in any particular area or group.

Constant vigilance has been maintained in Massachusetts since the outbreak of 1938 to detect additional cases of encephalitis due to the eastern virus. No additional cases have been discovered. No proved cases in horses have been found since 1939.

It is suspected that optimum conditions occurring in the Commonwealth in 1938 favored the spread of the virus from the reservoir host (as yet undetermined) to horses and to man. Certainly the suspected mosquitoes were present in abundance.

It is probable that another outbreak will not occur until the virus again builds up in a reservoir host simultaneously with an unusual abundance of the necessary mosquito vector. The information accumulated in the 1939 state-wide mosquito survey will then be put to practical use.

Summary

The public-health aspects of the six most important viruses that cause epidemic encephalitis are discussed, including the characteristics of the etiologic agents, their possible reservoirs, the usual vectors, the laboratory diagnosis and the possible means of control.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35241

PRESENTATION OF CASE

First admission. A twenty-six-year-old salesgirl was admitted to the hospital complaining of amenorrhea and swelling of her left leg.

Nine years before admission an appendectomy was performed at another hospital. Following the operation she developed swelling of the left leg. This continued up to admission, and was more severe after standing for long periods. Five years before admission the patient's twin sister, upon whom the patient was very dependent, died of "pancreatitis" after two years in a sanatorium for questionable pulmonary tuberculosis. During the following year the patient's weight fell from 145 to 115 pounds. Vague lower abdominal cramps appeared. She became nervous, and developed palpitation, weakness and fatigue. Four months before admission she suffered a severe episode of diarrhea lasting eight weeks, and had as many as ten to fifteen bowel movements for a twenty-four-hour period. There was no blood or mucus. The diarrhea slowly subsided, but there had been no menses since its onset.

Physical examination showed an extremely thin young woman. A Grade II blowing systolic murmur was heard over the precordium, loudest at the apex and second left interspace. A few moist rales were present at both bases. The abdomen was flat, with a right paramedian scar, which was slightly tender. There was a moderate white mucoid vaginal discharge and tenderness in the posterior cul-de-sac. There was +++ pitting edema of the left leg, and slight pitting edema of the right.

The blood pressure was 115 systolic, 80 diastolic. The white-cell count was 10,750, with a normal differential. The hemoglobin was 14 gm. per 100 cc. The urine was normal. The stools were repeatedly guaiac negative. A tuberculin test of 1:10,000 was negative. The sedimentation rate was 0.8 mm. per minute. The fasting blood sugar was 100 mg., and the total protein 4.5 gm. per 100 cc. The prothrombin time was 23 seconds (control, 18 seconds). The sodium was 145.2 milliequiv. and the chloride 100 milliequiv. per liter, the calcium 9.6 mg., the phosphorus 5.0 mg., and the nonprotein nitrogen eighteen to forty-three mg. per 100 cc.

A sigmoidoscopy was normal. A barium enema was negative; the terminal ileum did not fill. A barium meal showed a normal esophagus and stomach. In the distal portion of the jejunum or proximal ileum there was a delay in the passage of barium, and in this portion there were segments of markedly narrowed bowel in which the mucosal pattern was lost. Throughout the remaining ileum, including the terminal ileum, there were multiple similar areas.

During the first month of hospitalization she was essentially afebrile, and on a low roughage and high vitamin, calorie and protein diet she was comfortable except for abdominal distention.

A Miller–Abbott tube passed into the small bowel produced some relief. An ileotransverse colostomy without bowel resection was performed.

An x-ray film on the sixth postoperative day showed an area of increased density in the left lower chest, and a bilateral superficial-femoral-vein ligation was done under local anesthesia. No clots were found. After one month the patient was gradually weaned from intravenous feedings to a low roughage diet. Slight abdominal distention, cramps and occasional slight diarrhea appeared. She was discharged two and a half months after admission.

Second admission (eight months later). In the interval the patient had severe crampy diarrhea in bouts lasting two or three weeks, often watery but never bloody. She was admitted to the hospital for further study. The serum albumin was 3.76, and the globulin 1.41 gm. per 100 cc. There was no change in the x-ray findings, and she was discharged after a week in the hospital.

Third admission (fifteen months later). The patient had remained in fair health, had gained about 25 pounds and had married. She had intermittent

attacks of mild diarrhea (with a slight spot of blood on three occasions), but had periods lasting up to a month when she was entirely normal, with regular bowel movements. There was no abdominal pain. Her menses were now normal, occurring every thirty days and lasting four days. Her ankles and legs had been persistently swollen for a year, more severe toward the latter part of the day. The white-cell count, hemoglobin and urine were normal. A small-bowel series showed extensive areas of narrowing throughout the small bowel, the highest one beginning about 18 cm. from the ligament of Treitz. She was discharged after four days.

Fourth admission (fourteen months later). She was comfortable without change in her clinical picture until four months before admission, when she tried to manage a six-room house with stairs, and became fatigued. She noticed that the swelling of her legs increased to involve her thighs, hips and abdomen. Dyspnea on slight exertion, palpitation, sweating, and extreme fatigue appeared. Two months before admission a single dose of a mercurial diuretic resulted in a sudden diuresis of 35 pounds of fluid in two or three days.

On examination superficial edema was present below the ninth thoracic vertebra. There was ascites and ++++ edema of both legs.

The blood pressure was 132 systolic, 84 diastolic. The pulse was 96, and the respirations 18.

The white-cell count was 4500, with a normal differential. The urine was normal. The stools gave a + to ++ guaiac reaction. The serum albumin was 3.13, and the globulin 1.72 gm. per 100 cc. The alkaline phosphatase was consistently elevated above 10 units; the highest reading was 15.5 units. The cholesterol was 162 mg., vitamin A 1.1 units, and carotenoids 0.4 units per 100 cc. An oral glucose-tolerance test and a vitamin A test were normal.

She was afebrile, and under low salt and mercurial diuretics the edema subsided readily. She was discharged two weeks later on a high calorie, high protein, high vitamin, low salt diet.

Final admission (one month later). For the first week after discharge she felt well, and had no significant accumulation of fluid. In the subsequent three weeks edema fluid increased unremittingly in spite of vigorous mercurial therapy. In addition one barbiturate capsule nightly was prescribed by her physician.

There was marked edema in the lower half of her body, and ascites was present. The blood pressure was 110 systolic, 70 diastolic.

The white-cell count was normal. The hemoglobin was 10 gm. per 100 cc. The urine was normal. Admission stools were guaiac negative, and neutral fats and urobilinogen were normal. Combined fats were markedly increased. The serum alkaline phosphatase was 19.3 units, the serum albumin 2.62 gm., and the globulin 1.86 gm. per 100 cc. A cephalin-flocculation test was negative in forty-eight hours. The van den Bergh reaction was 0.2 to 0.6 mg. per 100 cc. The prothrombin time was 19 seconds (control, 16 seconds); the bromsulfalein test demonstrated 25 per cent retention of the dye in one hour. The fluid obtained on abdominal paracentesis was cloudy and yellow, with a specific gravity of 1.009, and contained 90 white cells and 2 red cells per cubic millimeter; a culture was sterile. The liver edge was palpable one fingerbreadth below the costal margin.

X-ray examination of the esophagus showed no varices. On mercurial diuretics and intravenous therapy, including albumin, the serum proteins were restored. The albumin was 4.49 gm., and the globulin 1.59 gm. per 100 cc. The edema persisted however.

The patient, always emotionally unstable, became depressed and during the fourth hospital month gradually became drowsy and unresponsive. A Chvostek sign appeared, but disappeared after intravenous calcium therapy. The coma persisted. She died five and a half months after admission.

Differential Diagnosis

Dr. Robert R. Linton: This patient had a number of admissions to the hospital. On the first admission she complained of amenorrhea for four months and swelling of the left leg for nine years. The complaint that she entered with does not strike me as being her chief trouble. I think that becomes more obvious as one reads more of the record. I would like to point out the statement, "four months before admission she suffered severe episodes of diarrhea lasting eight weeks." That is of extreme significance in relation to the remainder of the hospital course and, in fact, to the rest of her life. I am a little disturbed and completely puzzled by the death of her sister from pancreatitis when she was in a sanatorium with pulmonary tuberculosis. I have never associated pancreatitis with pulmonary tuberculosis; perhaps they do occur together.

When I read the record of this first admission I thought, of course, that this patient must have one of two things: regional ileitis or ulcerative colitis, because of the history of severe diarrhea. I will admit that one should not base one's diagnosis entirely on the history of diarrhea lasting for that length of time, but in view of it, I certainly was interested in these two parts of her gastrointestinal tract, the small bowel and the large bowel.

A barium enema revealed marked abnormality in the mid-small bowel down to the cecum, of sufficient severity to produce obstruction of the small bowel so that it was necessary to short-circuit the diseased segment by an ileotransverse colostomy.

A chest x-ray film was taken, and a diagnosis, presumably of pulmonary infarction, was made. Interruption of the femoral vein was carried out.

The fact that no clots were found is of no significance. I personally think if a patient is kept under observation long enough for clots in the common femoral vein to be found, it is comparable to a case of acute appendicitis in which one waits for the appendix to rupture before operating on it.

This case represents a chronic illness involving the intestinal tract. I believe I would leave out the stomach. We have very good evidence — clinically, by x-ray study and by direct inspection of the colon — that it was not involved, and that the disease was localized in the small intestine. It seems to me that this patient had been presented to me to discuss as a reminder of a patient that I had with a similar condition. Unfortunately, I did many more operations on my patient than this patient had, and despite them the disease progressed until the entire small intestine was involved. I do not believe that her amenorrhea had anything to do with the present condition. I think that it was probably secondary to her long-standing debilitating disease. This view is substantiated, I think, because the menses returned after her condition had improved following the ileotransverse colostomy. The edema of her leg, I believe, could have been secondary to an old thrombophlebitis of the lower extremities, which she apparently developed in the left leg at least. The swelling undoubtedly became more marked later on because of the low serum protein. We do not know too much about why people's legs swell, but I am sure that, if there had been obstruction of the lymphatics, the swelling would have been more marked. The left leg swelled, but the right one did not to begin with. I believe that both legs swelled after the femoral veins were interrupted because of the thrombophlebitis, which presumably developed following the ileotransverse colostomy.

It seems to me that this patient's condition is typical of regional ileitis. There are other conditions that one might consider, but I have to rule them out, simply because of ignorance regarding their clinical course. One is tuberculosis of the intestinal tract. I cannot see how it fits into the picture, although it is a possibility. Another is lymphoma of the small bowel. Again, I do not have sufficient evidence on which to base such a diagnosis.

I would like to see the x-ray films before going any farther.

Dr. Stanley M. Wyman: These are a few of the films taken when she first came in. They show a normal chest. The esophagus, stomach and duodenum are not remarkable, and the colon reveals no evidence of intrinsic disease. These are films of the small bowel taken over a three-year period, and they show the abnormal areas of small bowel, this being the terminal ileum, entering the cecum, and this being a loop of proximal jejunum. There are multiple areas of abnormal narrowing, with intervening, grossly dilated segments of bowel. The mucosal pattern is markedly thickened and grossly abnormal.

Dr. Linton: These x-ray findings, I think, bear out the written report, and I do not see how one can make any other diagnosis than regional ileitis, with massive involvement of the small intestine.

There are certain chemical studies that are of interest, some of which I am totally unable to decipher. The alkaline phosphatase, the vitamin A and the carotenoids do not help me much in making the diagnosis. To me, they represent abnormalities in bodily function secondary to long-standing illness. The most striking one, and the one that appears to me most significant, is the drop in serum protein, I suppose owing to the chronic condition. Although it was possible to bring this serum protein up to normal level temporarily, it was impossible to keep it there. Another interesting thing is the Chvostek sign, which is merely mentioned here; I believe that it appears in chronically ill patients with regional ileitis. The exact physiology involved, I am not sure about, but I have seen it in patients who had a large part of the small bowel removed. It apparently develops because of the inability to absorb calcium.

In conclusion, I believe that this patient had regional ileitis. She had a disease that we know very little about. If that is what it was, whether treated medically or surgically, the results are not encouraging. From my experiences, I would say that if one does an ileotransverse colostomy to short-circuit the diseased bowel distal to the uppermost lesions of small bowel, the chances of relieving the patient are slim, and the chances of curing her are nil.

Dr. J. H. Means: I saw this patient twice, in 1945 and again in 1949. We thought the early condition was regional ileitis and the leg condition a postphlebitic one, if I may use the term. Dr. Linton saw this patient in 1945. I consulted him and asked if it was subclinical elephantiasis, so called, with postoperative phlebitis, some years before, following appendectomy. I thought the obstruction was lymphatic or venous, or perhaps both. I saw her in the wards when she had swelling in both legs and marked hypoproteinemia, which we supposed was due to lack of small bowel. When I went off service, she was developing a psychosis, and she was transferred to the psychiatric service, where she died. That is all I know. Dr. Culver studied her case. Let us call on him.

Dr. P. J. Culver: I followed her for two years. When we first saw her she was in good health, in spite of x-ray evidence of widespread disease. Comments were made at the gastrointestinal rounds on how well she was doing. Then she had this dramatic change. She developed ascites of enormous proportion. It was impossible to explain why she had fluid retention from the diaphragm down and nothing up above. There was wasting of the shoulder girdle, arms and face. The edema and ascites did

not respond to mercurial diuretics. A review of her serum protein levels for the preceding two years made it impossible to attribute the ascites to hypoproteinemia, particularly since there had always been a low serum albumin. When we raised the albumin level with intravenous human albumin, we got a high serum level, but it did not relieve the ascites. Because we could not transfer the edema to the upper half of her body when the foot of her bed was elevated on shock blocks we thought that there must be a block in the inferior vena cava to explain what was going on. We called on Dr. Welch for an opinion, but he did not think caval obstruction was the cause of the ascites.

The liver chemical tests were of interest. She had a normal alkaline phosphatase initially, and it became elevated rapidly, enough to suggest an obstructive element in the liver. The remainder of the liver-function tests, with the exception of the bromsulfalein, were normal, indicating something obstructing the excretory mechanism in the liver. This is as far as we could go toward incriminating the liver. As for the hypocalcemia and its clinical manifestation, tetany, this was probably explainable on the basis that most of these people with regional enteritis have a terrific loss of insoluble calcium salts in the stool. An amazing fact was that, in spite of a damaged bowel, she absorbed vitamin A fairly well. Usually, we see a lowered absorption in this disease. The hypoproteinemia was due to the fact that she had lost so much albumin into the ascitic fluid, and into the edematous fluid, in addition to the fact, as Dr. Means has said, that she did not have enough small bowel to carry on.

Dr. Claude E. Welch: The question put up to me was whether the old thrombophlebitis could have progressed to the point where the inferior vena cava was completely obliterated and extended to the level of the liver, producing, perhaps, a Chiari syndrome and ascites, although it seems unlikely that that would be the cause. The patient had normal renal function, and the renal veins were functioning well. We considered further diagnostic measures in the way of venous catheterization, but she was so sick that we decided not to carry them out.

Dr. Linton: May I read the operating note at this stage? It is as follows:

> The small bowel was explored from the ligament of Treitz to the cecum. It was in no place adherent. Many typical lesions of chronic regional enteritis were present, interspersed between short segments of normal bowel. There was only one portion of the bowel that had an area longer than 10 cm. not involved in disease, and that was near the terminal ileum about 35 cm. above the cecum, where there was 30 cm. free of disease.

The extent of the disease found raises the question whether an ileotransverse colostomy was the best treatment for the extensive disease in the patient.

Dr. Culver: It was an emergency procedure because of obstruction. The surgeon's hand was forced. It was not an elective procedure.

Dr. Tracy B. Mallory: A small piece of information was left out of the record inadvertently. At one time when the medical service began to consider the possibility of liver disease, a liver biopsy was done and showed chronic passive congestion of severe degree.

Dr. Linton: I had mentioned that the liver-function tests had nothing much to do with her clinical symptoms, except that the liver was suffering as well as the rest, and I explained the increased bromsulfalein retention on that basis, rather than on that of primary liver disease.

Dr. Mallory: We have had a certain number of patients with ulcerative colitis and regional enteritis who, in the course of years, developed markedly fatty livers and, in some cases, definitely cirrhotic livers. That possibility was seriously considered here, but was apparently ruled out by biopsy.

Clinical Diagnoses

Inanition, with edema.
Regional enteritis.
Ascites of unknown cause.

Dr. Linton's Diagnoses

Regional enteritis.
Bilateral venous thrombosis of lower extremities.
Hypoproteinemia.

Anatomical Diagnoses

Regional ileitis.
Hepatic-vein and vena-cava thrombosis (Chiari's syndrome).
Central necrosis of liver, severe.
Ascites.
Edema of lower extremities, severe.
Multiple pulmonary emboli, microscopic.
Operative wounds: ileotransverse colostomy and ligation of superficial femoral veins.

Pathological Discussion

Dr. Mallory: Post-mortem examination disclosed very severe regional ileitis. There were innumerable areas of involvement of the small bowel, some of them as short as 1 cm. in length and some as long as 10 cm. The highest one, as the x-ray report stated, was only 30 cm. beyond the ligament of Treitz, and the lowest one extended down to the ileocecal valve; so that the patient had really very little intestine except a duodenum and 30 cm. of jejunum that could be considered normal. We did find a thrombus in the inferior vena cava, which was about 10 cm. in length. It started above the level of the renal veins, which were entirely uninvolved, and extended up above the mouth of the hepatic vein and then there was retrograde thrombosis of the hepatic veins throughout the liver, even down to the very small ones, making a characteristic picture of so-called Chiari's syndrome. This was quite consistent with the liver biopsy. The finding of chronic passive con-

gestion of the liver in the absence of heart disease suggests obstruction between the level of the hepatic vein and the right auricle at some point. The liver itself showed rather extensive secondary degeneration, part of it looking simply like extremely marked chronic passive congestion and part of it being a picture of incomplete infarction. The age of the intrahepatic thrombi was variable. Some of them seemed quite fresh, and others showed marked organization and must have been present weeks — and perhaps months or more.

DR. CULVER: Do you think this could explain the ascites that had been present for six months?

DR. MALLORY: It is hard to estimate the age of these thrombi with exactness. An otherwise healthy person will organize a thrombus comparatively rapidly; a very ill patient may require two or three times as long to effect the same amount of organization. It is quite possible that these thrombi are of longer duration than one would estimate from ordinary criteria.

DR. CULVER: Is not the amount of ascites in the case unusual for regional ileitis? In fact, I have not seen a case with more than minimal fluid in the abdomen. Could the ascites be explained by blockage of the lymphatics with an infiltrative reaction throughout the small bowel rather than any other cause, such as liver disease, portal hypertension or hypoalbuminemia?

DR. MALLORY: I had not thought of that possibility but did not see any striking evidence of lymphatic dilatation in the bowel, and I would be more inclined to think it was due to portal hypertension.

DR. LINTON: The vena cava was not completely occluded?

DR. MALLORY: No; perhaps only one third.

DR. WELCH: Do you think this was the end result of ascending thrombosis of the vena cava, or possibly that the thrombosis in the liver was more or less simultaneous? The thrombi met in the middle, which is a peculiar picture.

DR. MALLORY: It is possible; I cannot say with certainty whether the thrombus started in the hepatic vein or in the vena cava.

DR. LINTON: Perhaps it was started by the biopsy!

DR. MALLORY: It is frequently recorded in cases of Chiari's syndrome that there is thrombosis both in the vena cava and in the hepatic vein.

CASE 35242

PRESENTATION OF CASE

First admission. A twenty-seven-year-old photographer entered the Out-Patient Department complaining of recurrent attacks of right-flank pain.

Five years before admission, he had an attack of right-sided pain that was very severe and forced him to go to bed. The pain was situated on the lateral side of the right thorax, from the level of the sixth rib down into the flanks and around to the back. It occasionally radiated to the region of the anterosuperior iliac spine, but never to the left side, shoulder, scapula or umbilicus. It was steady and sustained, never colicky. The pain was not related to meals. There was no headache or urinary symptoms. His appetite had diminished. The pain subsided after two weeks, but a residual soreness persisted. Attacks recurred about once each month, lasting one or two weeks. The pain was so disabling that he was unable to work and was virtually an invalid. There was no weight loss. The more recent seizure started two weeks before admission.

He had scarlet fever at six years of age, but no cardiac or renal sequelae were recalled. At the age of twelve, he had rheumatic fever, and was confined to bed at home for one year. There were several recurrences until fifteen years of age. Four years before admission he entered another hospital with pneumonia. For many years, he had been aware of vigorous heart action, especially at night, when he was disturbed by the shaking of the bed with each heart beat. He was able to climb one flight of stairs rapidly without feeling excessively breathless. He slept lying flat. There was no ankle edema.

Physical examination showed a pale, asthenic, well nourished man. The heart was markedly enlarged, the apical impulse being prominent and visible in the seventh interspace in the axillary line. Rough and blowing systolic and diastolic murmurs were loudest at the aortic area, and radiated to the neck and the apex. The second pulmonic sound was faint. The rhythm was regular. The lungs were clear and resonant throughout.

On abdominal examination two points of deep tenderness were found: in the anterior right flank about two fingerbreadths below the costal margin extending posteriorly for an area about 15 cm. in diameter, and in the right lower quadrant just above Poupart's ligament.

The blood pressure was 180 systolic, 30 diastolic.

The white-cell count was 10,200, and the red-cell count 5,300,000. The urine had a specific gravity of 1.012 and gave a +++ test for albumin; the sediment contained occasional white cells and hyaline and granular casts. A culture was negative, and a concentration test reached up to 1.015. The nonprotein nitrogen was 33 mg. per 100 cc. The phenolsulfonephthalein test showed 15 per cent excretion in fifteen minutes, and 50 per cent within the first hour. An electrocardiogram was abnormal, suggesting left ventricular strain. The QRS complex was slurred and widened to 0.10 second. There was slight left-axis deviation, with sagging ST segments and inverted T wave in Lead 1 and diphasic T wave in Lead 2; the PR interval was 0.20 second.

A chest x-ray film showed clear lung fields and a markedly enlarged heart, chiefly in the region of the left ventricle. There was a small amount of fluid in both costophrenic angles.

Intravenous pyelography showed no definite filling of the kidney, pelves or ureters. Some dye was seen in the bladder after twenty minutes. On retrograde pyelogram and cystoscopy only the right meatal orifice was found. Retrograde filling on this side showed a short ureter, but the renal pelvis was superimposed on the mid-sacrum.

Under observation as an outpatient, acute episodes of pain recurred, and eleven months after his first examination he was admitted to the hospital. The previous findings were confirmed, but since his pain diminished in intensity he was discharged eight days later to return at the onset of another attack for a diagnostic novocain block. Another retrograde pyelogram confirmed the previous finding of a single pelvic kidney. The calyxes appeared small but were otherwise normal.

Second admission (eight months later). The patient returned because of an acute attack. Right paravertebral novocain injection was employed, and the pain was relieved temporarily.

Third admission (one year later). A right lumbodorsal sympathectomy was done, with immediate relief of pain.

Fourth admission (two years later). The patient complained of severe pain, localized to an area 15 cm. in diameter just to the right of the spine and below the scapula, requiring demerol or morphine for adequate relief. In addition, in the two years after operation dyspnea on exertion had increased, and on repeated occasions he was awakened by a smothering sensation, which forced him to sit upright and go to an open window. The heart was increased in size over previous examinations, and loud harsh systolic and diastolic murmurs were heard at the base. Slight presystolic accentuation at the apex and a mid-diastolic rumble were noted. A normal sinus rhythm (rate of 90) was present. The blood pressure was 190 systolic, 50 diastolic.

The sedimentation rate was increased to 1.1 mm. per minute. Moderate members of *Staphylococcus albus* and a few colon bacilli were cultured from the urine. The nonprotein nitrogen was 48 mg. per 100 cc., and the blood chloride was 111 milliequiv. per liter. An electrocardiogram showed a PR interval of 0.20 second and prominent S wave in Lead 2; the T waves were inverted in Lead 1, diphasic in Lead 2 and upright in Lead 3. Sweating and skin-temperature tests demonstrated complete sympathetic regeneration. A Graham test was negative. Therapy included digitalization, a large fluid intake and demerol for pain.

After two months the patient was transferred to another hospital for chronic convalescent care, and remained there for four months.

Fifth admission (seven months later). The patient was readmitted complaining of recurrent pain in the right posterior thorax. The physical findings included marked pallor and forceful arterial pulsations in the neck. The heart was markedly enlarged, the point of maximal impulse being at the anterior axillary line in the seventh interspace; a protodiastolic gallop was present at the apex. The following murmurs were found: a Grade III, rough, aortic systolic murmur, a Grade III, long diastolic blow at the base, left sternal border, apex and axilla and a Grade II, rather high-pitched apical systolic and an apical diastolic rumble. The lungs were clear. The liver edge was palpable at the costal margin, with tenderness. There was slight ankle edema.

The blood pressure was 230 systolic, 0 diastolic.

The sedimentation rate was 58 mm. in sixty minutes. The red-cell count was 4,280,000, with a hemoglobin of 9.5 gm. per 100 cc. The nonprotein nitrogen was 78 to 125 mg. per 100 cc. The chloride was 109 milliequiv., and the carbon dioxide 16.6 milliequiv. per liter, and the creatinine 4.2 to 4.9 mg., the calcium 7.5 mg., and the phosphorus 5.5 mg. per 100 cc.

Final admission (three years later). The complaint at this time was during the interval in which the patient was seen frequently as an outpatient and inpatient. His complaints were right-chest pain (relieved only by sedation), dyspnea and ankle edema, and repeated severe epistaxes requiring packing and blood transfusions. On examination bilateral moist rales were heard at both bases, more marked on the right, with slight dullness on the right. Right-upper-quadrant tenderness in the abdomen was noted. There was a +++ pitting edema behind the malleoli. The blood pressure was 240 systolic, 40 diastolic.

The white-cell count was 21,100, and the hemoglobin 7.2 gm. The specific gravity of the urine was 1.010, with a +++ test for albumin and a + test for sugar. Many white cells and amorphous granular material were present in the sediment. The nonprotein nitrogen was 200 mg., the fasting blood sugar 105 mg., and the total protein 6.1 gm. per 100 cc., and the carbon dioxide 10.5 milliequiv., the sodium 124.5 milliequiv., and the chloride 90 milliequiv. per liter.

The patient developed progressive respiratory distress, with increasing moist rales in both lungs. He died on the seventh hospital day.

Differential Diagnosis

Dr. Howard B. Sprague: Those who took care of this patient had the opportunity of watching him for seven years. I have had less than one day to consider this situation. I hope they were happier about it than I am. It does seem, however, that there is enough in the history to explain why the patient died, but I am not sure what caused his

prolonged disability — namely, this peculiar kind of pain.

To begin with, he began to have trouble when he was twenty-two years old, and he had for about half the time in the next seven years recurring right-flank pain, which lasted one or two weeks at a time and came on about once a month. That leaves him not much free time without pain. I assume from this history that he had rheumatic heart disease with aortic involvement — aortic regurgitation and some degree of aortic stenosis. There was a questionable mitral diastolic rumble, which could have been an Austin–Flint murmur, but on a statistical basis I suppose we would say that there was both mitral and aortic involvement. There was apparently congenital absence of the left kidney and a solitary pelvic kidney on the right side with a short ureter, which would indicate that it was a developmental affair. There was normal rhythm in the heart — that is, no auricular fibrillation, and predominantly an aortic lesion. This does not influence us toward the thought of multiple embolic phenomena. Certainly a patient cannot have emboli every two or three weeks for seven years, I would think, without having more to show for it. The pain was relieved by both the paravertebral block and the right lumbodorsal sympathectomy. Dr. J. C. White is here and will presumably tell us about this later. But since nothing is said in the history about whether anything peculiar was seen when the operation was performed, I shall assume that probably nothing was seen. He had progressive anemia, progressive renal failure, uremia and a questionable urinary infection. The epistaxis was presumably on the basis of hypertension and renal state, although one has to think of active rheumatic fever and nosebleeds.

Let us consider this pain, which had a distribution as high up as the sixth rib in the back but which seems mostly to have been right-flank pain and below the costal margin, at times to the crest of the ilium. It seems to have been more below the ribs than up in the chest, and there is nothing in the x-ray report to suggest anything wrong in the chest. There does not seem to have been anything on which to base a suspicion of gall-bladder or liver difficulty. Of course, acute recurrent liver congestion that occurs in mitral stenosis has to be thought of too, but this does not quite seem like that. He did not have a large tender liver related to the attack. The Graham test was negative. The distribution of this pain would seem to me to be renal in its position, and I am interested to know, since he had only one kidney and it was down in the pelvis, whether he maintained the ordinary renal distribution of pain, if he had trouble with that kidney.

Perhaps Dr. White would be willing to answer that for me.

Dr. J. C. White: I would expect he had, because it would drag the nerve supply with it. When I was working in the Anatomical Laboratory of Professor Hovelacque in Paris, I dissected a cadaver with a very similar pelvic kidney, which derived its blood supply from the common iliac artery. The nerve supply came down from above in the usual fashion.

Dr. Sprague: That was the way I had argued — perhaps the nerve supply would be more likely to maintain its normal relation with the kidney than the blood supply. If we think in terms of development of the kidney in that area, and its failure to "ascend," it was actually being dragged down by the short ureter, which did not allow its blood supply to develop normally. I see nothing in the history to suggest urinary obstruction — at least there was nothing resembling a Dietl crisis, and urologic study would not indicate dilatation of the kidney. I have been informed that the x-ray films are not available at the present time, but that is the way that I interpret it from the history. So I am going to say, in spite of congenital anomaly of the kidney, that there was rheumatic rather than congenital heart disease, with aortic and perhaps mitral involvement, and that there was a progressive change in this solitary developmentally abnormal kidney in the nature of a true nephritis, perhaps of vascular origin with secondary infection. He had uremia and mounting hypertension, and then, to explain the pain, I am forced to fall back on the relation between the heart, aorta and the abnormally placed kidney. I was intrigued to think about a multitude of vascular anomalies commonly occurring in this region to account for this as being vascular pain in some way, probably radiating over an extensive pathway, but it may be that the kidney was so placed in relation to the aorta, and bound down by adhesions, that the severe aortic regurgitation acted in some way to irritate the attendant nerves. I would like to find out what was really wrong with this patient.

Dr. White: The urologists believed that this patient did have an ectopic kidney. That was fairly well proved. We asked them if they would do a retrograde distention of the kidney pelvis and single ureter, but they were reluctant to do so, because it was his only kidney. That would have proved whether the pain of which he was complaining in his paroxysms was of renal origin. Be that as it may, he did not have pain in the flank or groin after operation. When he came in two years later the urologists were willing to pass a ureteral catheter up to the pelvis and distend it; they found that it produced no pain. It was therefore evident that the kidney was denervated and that the pain he was having in the chest was not of renal origin. The operation was similar to that done for hypertension, the twelfth rib being taken out. I removed about 5 or 6 cm. of the major

splanchnic nerve and the sympathetic ganglionated chain from the tenth thoracic to the second lumbar segment, which would be sufficient to denervate the normal kidney. I wonder if Dr. Sprague has any explanation why the patient continued to have right thoracic pain? I have seen one patient with a tense liver capsule from cardiac failure who had pain of this sort, and I have also seen continuous discomfort in patients with active rheumatic heart disease. I remember one such case that Dr. T. Duckett Jones and Dr. Edward F. Bland had at the Good Samaritan Hospital, and they asked me to do a paravertebral injection. The patient had intermittent angina pectoris and steady pain in the right chest. Both types of pain were relieved following alcohol injection of the cardiac nerve.

DR. SPRAGUE: That was probably a mitral case.

DR. WHITE: The patient, a young woman, as I recall her, had aortic regurgitation, but I do not remember whether she had mitral disease as well.

DR. WILLIAM CHAPMAN: As I recall, the first pain in the case under discussion was located between the vertebra and medial border of the scapula and was reproduced by injection of 6 per cent saline solution in the same segment on the other side, which suggested a cerebrospinal or somatic pain. One expected, as Dr. Sprague did, that it was related to the grossly enlarged heart, and it was difficult to see how the enlarged heart could be pressing on the right side.

DR. SPRAGUE: I was trying to get out of my dilemma by saying that by sympathectomy we pushed the pain higher as we push anginal pain to the other side in some sympathectomized patients.

DR. WHITE: Yes; anginal pain may appear on the opposite side, and occasionally it may shift up into the jaw.

DR. SPRAGUE: True, but I was not quite clear about the amount of regrowth in the sympathetics.

DR. WHITE: I think that very often regeneration of peripheral vasomotor fibers, and much more rarely of the visceral nerves may occur.

CLINICAL DIAGNOSES

Uremia.
Chronic nephritis in single congenital ectopic kidney.
Rheumatic heart disease.

DR. SPRAGUE'S DIAGNOSES

Rheumatic heart disease, aortic regurgitation and stenosis and slight mitral stenosis.
Congenital solitary pelvic kidney, with renal pain.
Chronic glomerulonephritis and uremia.

ANATOMICAL DIAGNOSES

Rheumatic heart disease, aortic stenosis and regurgitation.
Adhesive pericarditis, chronic, with calcification.
Congenital anomaly — single pelvic kidney.
Chronic glomerulonephritis.
Hyperplasia of the parathyroid glands.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: I think our autopsy findings were very much like Dr. Sprague's clinical diagnosis. We can explain the cause of death very readily; I am not sure that we can explain the cause of pain. The patient had the largest heart that we have ever seen in this laboratory (it weighed 1500 gm.), and he evidently had three causes for that enlargement. One was a severe rheumatic involvement of the aortic valve, with both regurgitation and stenosis. The mitral valve was essentially normal. He also had an adherent pericarditis, with considerable amounts of calcification in the pericardium. He unquestionably had hypertension on the basis of renal disease.

There was only one kidney, which lay in the pelvis and had a short ureter. The kidney had two arteries, the source of one of which was at the bifurcation of the iliac vessels, but the other smaller artery was not traced to its source. The single kidney weighed only 110 gm. and was scarred and granular, without, however, any dilatation of the pelvis. The microscopical sections showed an old, severe glomerulonephritis, so that there is ample explanation for renal failure. He had moderately enlarged parathyroid glands, as one would expect with such long-standing renal insufficiency. We found no involvement of the mediastinum that we could recognize, and except for the large heart and the adherent pericardium there was nothing in the thoracic cage that would explain the later episodes of pain in the thoracic region.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Owned by the Massachusetts Medical Society and Published Weekly under the Jurisdiction of the Committee on Publications

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Subscription Terms: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

A WILLING PARTNERSHIP

It is an accepted thesis that the most important consideration in selling the idea of good medical care to the American people is to make them aware of what constitutes such care, and then to deliver it. They must be informed of its limitations as well as its accomplishments. They must know what it is worth in dollars and cents, and why. They must be directed toward the fairest and most economical way of meeting those costs.

From here on, mystery and magic, the ancient cloaks of medical grievance, are out.

Already, thanks to the kind and well intended efforts of various persons and organizations working for the adoption of compulsory health insurance, the people are taking great interest in the quality and distribution of medical care. The indications are that with increasing knowledge they are making up their minds in favor of free enterprise and voluntary systems of health insurance in which they can determine their own stake. They are willing to go into partnership with their doctors.

The continuing education of the public along these lines has been assumed by the medical profession, which is in the best position to carry on such a course of instruction. Its extension must be in the hands of informed laymen whose interests are obviously those of the public that they represent.

Every physician, nevertheless, as was indicated at the gathering of physicians and representatives of woman's auxiliaries held in Boston on May 1, is an unofficial spokesman of his profession. Armed with the material that is directed to him through organized professional channels, he is delivering to his own segment of the public accurate information for further intelligent distribution.

While words must constitute the greater part of the ammunition in this battle for the continuance of an improved American way of life, consistent with liberty and the pursuit of happiness, words are fortunately not often lethal. They have their dangers, however, and too heavy a barrage must not be laid down. The old refrain "It's a terrible death to be talked to death" must still be borne in mind. There is a limit even to the amount of propaganda that one can sustain, and survive.

EPIDEMIC ENCEPHALITIS IN RETROSPECT

Elsewhere in this issue of the *Journal* Ayres and Feemster present a nine-year to ten-year recheck on all the children who survived the 1938 outbreak of eastern equine encephalomyelitis in Massachusetts. The fact that only 1 child out of 34 is known to have come through unscathed is indisputable evidence of the violence of the infection with the virus of this particular disease. Twenty-five of the cases ended fatally, and 7 of the 9 survivors have varying degrees of mental and physical handicaps.

It is fortunate that a virus that causes such a stormy course seldom spreads to man. When it is considered that 70 per cent of human beings and 90 per cent of horses die of the infection with the

eastern virus, compared to only 10 per cent of the human beings and 20 to 30 per cent of the horses with the western virus, it can be understood why large outbreaks can occur in the western part of the country, where the latter is the predominating variety, whereas only a few isolated cases or small outbreaks occur in the eastern areas, where the eastern virus is more frequently found. An etiologic agent that kills off most of the hosts attacked has difficulty in surviving.

The progress report in this issue summarizes present knowledge of the public-health aspects of the six more important viruses that cause epidemic encephalitis. Much additional information is needed to provide a clear understanding of the peculiar geographic localization, not only of the eastern and western viruses but also of the virus of the St. Louis encephalitis. All these diseases can be transmitted by insect vectors prevalent in the eastern United States as well as in the West, but up to the present time most of the outbreaks have occurred west of the Mississippi River.

A state-wide mosquito survey carried on in 1939, as a consequence of the 1938 outbreak, furnished much useful information regarding the varieties and habits of the mosquitoes in Massachusetts. This information will be valuable if another outbreak of eastern equine encephalomyelitis should occur, or if one of the other two viruses should be transported into this area.

—WHO HELP THEMSELVES

The American Red Cross performed such a variety of heroic services to the country during the war that it is hard to bear in mind the continuing value of some of them in the uneasy days that have succeeded the conflict. Of special importance in this respect is the training in the elements of home nursing that so many women received in those days. This training, less dramatic than first aid, was equally useful; less impressive than automobile repairing, it was more practical.

It should be a source of comfort in innumerable households as well as a contribution to the sense of security of many family physicians to know that the Home Nursing Courses of the Red Cross are not only continuing but expanding their services.

These courses are divided into two units, one on the care of the sick and one on mother, baby and family care. Each, independent as a unit although complementary to the other, consists of six two-hour lessons. They are taught by qualified graduate nurses. Elementary as they are, they may serve the purpose of turning a willing but ineffective member of the family into one capable of caring for patients who are not critically ill or completely helpless, and for giving adequate attention to mothers and babies. Such service, particularly as it may be augmented by the visiting nurse, can save many hours of expensive hospitalization and in many instances render unnecessary the search, so often fruitless, for a high-priced nurse willing to go into the home. Information regarding the courses may be obtained from any Red Cross chapter.

The paradoxical situation exists today in which the products and the skills of science and industry are virtually beyond the reach of a considerable proportion of householders. Service of any nature has become so dear or so scarce that a return to the days of personal self-reliance is almost inevitable. More and more must the homeowner of today learn through necessity to saw a straight line and to set a pane of glass.

In matters ranging from replacing buttons to patching pants; from putting pans under leaking roofs to conquering the complexities of bed baths, the old adage that God helps those who help themselves is being reaffirmed. The hand-worked sampler may have given way to offset printing, but Home Sweet Home, while still the dearest place on earth, can be made a little less expensive if every member of the family makes some personal contribution!

GRIM REAPER

Traffic deaths in the United States, according to The Travelers Insurance Companies, dropped 1 per cent in 1948. The total, in round figures, was 32,200 as compared with 32,500 in 1947. Personal injuries, however, increased 8 per cent to a total of 1,471,000, the 1947 figure having been 1,365,000.

Pedestrians, apparently, can jump faster, even if no farther.

More than a third of the deaths and nearly a quarter of the injuries were attributed to excessive speed, and this has been the important factor in recent years. Like Mr. Toad of Toad Hall, too many human beings experience changes in personality when under the influence of intoxicating motion. This applies particularly to the more adventurous, less cautious ages between eighteen and twenty-four, which are responsible for more than their share of both deaths and injuries.

It is difficult to know surely whether American automobile manufacturers are creating or supplying a demand when they continue to produce increasingly speedy and increasingly costly motor cars. Every conservative instinct cries out for the opposite policy, but it appears that the majority of democracy's fellow travelers live literally for the moment only.

MASSACHUSETTS MEDICAL SOCIETY

Presidential Address

Your vote of confidence in me is deeply appreciated. No member of the Massachusetts Medical Society receiving this great honor could possibly fail to be duly impressed. I know that there are many among you more deserving of this recognition than I. Having observed the work of the Society closely for many years and pursuing a careful study of its activities during the past twelve months, I realize the tremendous responsibility you have placed upon me. It is with full awareness of my own inadequacies that I accept this position as your moderator. I assure you that I am fully cognizant of the fact that this is no dictatorship — no one-man show. I earnestly beg of you to give the Society your best effort, and to give me your guidance and counsel throughout the coming year. We must work in close co-operation and in harmony, without selfish interests but with a steadfast purpose for the good of the Society as a whole and for the benefit of humanity.

I suppose every president who has preceded me has believed that his specific term of office came at a critical period. Doubtless many have regarded their terms as offering an unparalleled opportunity for the Society to turn its attention to the problems of the moment. Always there have been emergency measures of one kind or another to be dealt with, and always, as now, the constant desire to advance medical education and improve medical care. This attitude, which was the prime motive in the organization of the Society one hundred and sixty-eight years ago, has never changed. There has been steady progress in the past so that we can well take pride in the quality of medical service now available in this state and in this nation. We cannot accept a complacent attitude concerning these matters. The hope is that never in the history of the Massachusetts Medical Society will there be a smug feeling of satisfaction regarding our accomplishments that will in any way detour us from the straight and narrow road in seeking a higher level of service.

The serious national problems before us are demanding our constant attention. Our educational program is going well, and the people of this country are being awakened to their situation. It is apparent that they are eager for knowledge concerning all matters pertaining to their health and to their rights as citizens. Over 600 organizations in the United States have passed resolutions opposing compulsory health insurance. This is encouraging, and the effort expended appears to have been worth while. We must not allow these favorable reports to lull us into inactivity however. We must learn and dispense the true facts with constant vigilance and without interruption. We have the satisfaction of paying for this program ourselves even though we are also paying through taxation, in part, for the propaganda of our clever opponents.

We shall need to marshal our strongest forces on the national battlefront for some time to come. We have, however, reserves that are available for a continuation of our efforts to advance the art and science of medicine. These are and always have been carried out for the prevention of disease, for the improvement of health and for the relief of the sick.

Your many committees set up to study our various problems and to expedite the responsibilities of the Society have been carefully evaluated. Some whose purposes have been accomplished are recommended for discharge. The personnel of new ones endorsed by you tonight will be announced after due thought and consideration.

You have approved of the recommendation of the Committee on Public Health to appoint a subcommittee for the purpose of developing pilot diagnostic clinics. It is my understanding that this is to be done in co-operation with the various specialty groups already working along these lines, and that such clinics are to be staffed by the medical personnel of the district in which they are established and in already existing community hospitals. The beneficial effects already demonstrated by

the Tuberculosis League, the State Cancer Society, the Committee on Diabetes and the Heart Association are well known to you. If the mechanism of clinics for general examinations can be satisfactorily worked out for all concerned, we shall have made a great forward step. It is requested that those of you who are skeptical of such a venture offer constructive criticism and lend your aid to this endeavor.

American medicine has been severely criticized about the inadequacies of medical care. Much has been said regarding the shortage of doctors. We are told that, in certain localities at least, emergency medical service is difficult to obtain, particularly on week ends and holidays as well as at night. We have also had reverberations that are not to our credit regarding the charges made, in some instances, for professional services rendered. This appears to be a proper time to consider seriously these problems and first of all to find out what the true situation is and to see what needs to be done about it. We realize that such complaints are greatly exaggerated and that an isolated instance may make a bad impression for the Society as a whole. On the other hand it is to our best interests to rectify these errors if they exist.

Without any doubt, a nation-wide survey concerning the health needs of people should be made. It is hoped that a commission set up along the lines of the Hoover Commission will be established to carry out such a study. Since it will be necessary for each state to participate in such a program, it seems that we should be in a better position if we considered looking into our own situation now. It would be necessary to have each district participate in this procedure with the eventual co-ordination of the facts. What we can do about inadequacies, if they exist, will be a matter for future consideration.

I have had the privilege during the past year of attending the majority of the meetings held by your various committees. The sacrifice of time and the tedium of travel do not interfere with the seriousness of purpose that these men display. The Society as a whole and the citizens of the state it serves should be duly grateful for such devoted service. Since there are so many committees already, you may not be willing to support me in the request I make for one more. I hope, however, that you will and that we can start our survey of the availability of adequate medical care in the Commonwealth.

In conclusion, I should like to make a strong appeal to the district presidents. It is obvious to all that there are times when it is impossible for a committee man to attend a stated meeting of his committee. It appears, however, that these absentees are more apt to be representatives of certain of our districts. I am sure that if the district president would study the situation and more carefully make his appointments we should have a better representation. We want the advice and counsel from all areas and urge that every effort be made to make our society truly representative.

Again, I thank you for your confidence in me and once more ask for your help and counsel, and for your charitable and lenient attitude when my procedures fail to meet your full approval.

ARTHUR W. ALLEN

CORRESPONDENCE

MAKE HASTE SLOWLY

To the Editor: There is no doubt that most doctors are opposed to President Truman's plan of health insurance. But how many of them failed to vote against the politicians who have undertaken the transformation of our republic into a socialized democracy is of pertinent interest.

As members of a learned profession, we should naturally embrace the conservative. Whatever socialistic changes we may happen to favor we should prefer to have come gradually. We certainly can hardly approve of the rate at which stark socialism has been growing in this country. We are well aware of the waste and inefficiency of the divers mushrooming bureaus, which tend to destroy our individuality and to weaken our souls.

In our next political campaign, may it not be more discreet for us to resist socialism in general as individuals rather than as a group exposing our profession to the charge of selfishness and trade-unionism?

G. W. HAIGH, M.D.

Worcester, Massachusetts

NOTICES

ANNOUNCEMENT

Dr. Donald T. Chamberlin announces the removal of his office from 422 Beacon Street, Boston, to 1180 Beacon Street, Brookline.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 21, at 12 noon. Dr. John G. Downing will speak on the subject "Local Therapy in Dermatology."

Physicians are cordially invited to attend.

94TH INFANTRY DIVISION LECTURES

The 94th (Bay State) Infantry Division is sponsoring a series of monthly lectures by prominent physicians in their respective specialties. The fifth lecture will be held in the auditorium of Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, June 28, at 8:00 p.m.

Dr. Henry M. Lemon, Captain, Medical Corps Reserve, will speak on the subject "Recent Advances in the Diagnosis of Malignant Disease."

All interested physicians, whether reserve officers or not, are cordially invited to attend this carefully planned program. Reserve officers will be given one point credit. Excellent films will also be shown during this period.

(*Notices concluded on page xi*)